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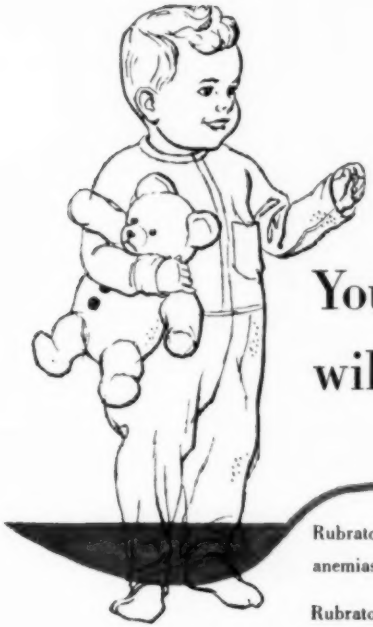

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South African Medical Journal
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AUTO-ANTIBODIES IN THE PATHOGENESIS OF DISEASE

A PRELIMINARY STUDY OF AUTO-SENSITIZATION OF RED CELLS IN VARIOUS DISEASES

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and
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The hypothesis that auto-antibodies are concerned in the pathogenesis of many diseases of somewhat obscure aetiology was recently discussed.[1] It was suggested that tissue cells may be altered and so made auto-antigenic by the action of bacterial toxins, chemical and physical agents, and by the presence of intracellular parasites, including viruses and protozoa. It was postulated that these auto-antigens stimulate the formation of the corresponding auto-antibodies. It was noted that there is now convincing evidence that auto-antibodies are responsible for acquired acholuric jaundice.[2] Previously it had been suggested that auto-antibodies are responsible for this and for other blood dyscrasias including splenic leucopenia and acquired thrombocytopenia.[3] There is also evidence incriminating auto-antibodies in the pathogenesis of several diseases of the central nervous system, including acute disseminated encephalomyelitis[4] and sympathetic ophthalmia,[5] of glomerular nephritis[6, 7] and of several of the so-called collagen diseases including rheumatic fever,[8] acute disseminated lupus erythematosus,[9] dermatomyositis, and of many skin diseases including exfoliative dermatitis, scleroderma and possibly of some cases of the Stevens-Johnson syndrome.[1] This evidence is not yet entirely convincing, but it certainly is suggestive and emphasizes the need for further study of the immunological reactions of these diseases.

One of the difficulties is to devise tests to detect the presence of auto-antibodies to cells other than red cells. In cases of acquired acholuric jaundice antibodies to the red cells may be demonstrated directly by the agglutination of isogroup red cells (suspended in saline or sometimes only when suspended in albumin) by the patient's serum. Sensitization of the red cells of the patient by immune globulin may also be demonstrated by the Coombs test.[10]

For this test an antiserum against human serum is prepared in rabbits by a suitable course of inoculations. When this course is completed, the rabbits are bled and the serum separated. This serum is then absorbed with red cells to absorb out anti-red cell antibodies. There remains a specific anti-human serum antiserum which is used in the test. This test, by means of this anti-human globulin serum prepared in rabbits, detects the presence of immune globulin adhering to the sensitized red cells.

More recently several other methods of testing for sensitization, including the use of enzymes such as trypsin, have been introduced. These newer tests occasionally demonstrate antibodies not revealed by the Coombs test.

It was considered possible that auto-antibodies against various tissue and organ cells, as well as affecting the cells primarily concerned, might also involve red cells. Thus it seemed to be worthwhile in cases of the diseases in which auto-antibodies were suspected of playing a role, to investigate whether sensitization of the red cells occurred. Accordingly, a systematic study of the sensitization of the red cells of patients suffering from a variety of diseases was undertaken. This paper records the results of this study.

METHOD

The blood from the patient was collected in a sterile tube without anticoagulant. The serum was separated. A 2% suspension of red cells in physiological saline was then made as for testing for Rh antigens. Six drops of this suspension were placed in a centrifuge tube and washed three times in 10 c.c. physiological saline. The washed cells were suspended in physiological saline to make a 2% suspension. These cells were then tested in tubes with two dilutions of anti-human serum, the dilution used depending on the titre of the rabbit antiglobulin serum; a control tube was included in every case. The mixtures of red cells and serum were incubated at 37°C for one hour. Reactions were then read macroscopically and confirmed microscopically. The results were usually clear, but in an occasional case, where the reaction was so weak as to be of doubtful significance, the result was given as negative.

Some tests were also carried out on a tile using somewhat stronger suspensions of washed red cells, but for systematic work, where the result is not required urgently as it is in the case of testing blood from the newborn in cases of suspected haemolytic disease, the tube test was preferred and used in the routine procedure.

The results are given in Tables I-V.

COMMENT

From these Tables it will be seen that the Coombs test for sensitization of the red cells gave negative results in the majority of cases of the acute and chronic infective diseases. There is the notable exception of syphilis in which it was found that over 50% of the sera giving strongly positive Wassermann reactions also gave a positive

Coombs test. The meaning of this finding is not known and obviously requires further study.

TABLE I: BLOOD DISEASES

Disease	*Number Tested*	*Cold Agglutinins* 1:16 +	—	*Coombs Test* +	—
Haemolytic anaemia					
Acquired type ..	12	4	8	4	8
Congenital type ..	8	0	8	0	8
Cooley's anaemia ..	1	0	1	0	1
Aplastic anaemia ..	5	1	4	1	4
Haemophilia	3	0	2	0	3
Thrombocytopenia ..	2	0	2	0	2
Tropical eosinophilia ..	1	0	1	0	1
Agranulocytosis ..	2	0	2	0	2
Glandular fever ..	4	1	3	1	3
Lymphatic leukaemia	1	0	1	0	1
Myeloid leukaemia ..	3	0	3	1	2

TABLE II: CONDITIONS AFFECTING THE BLOOD VASCULAR SYSTEM

Clinical Diagnosis	*Number Tested*	*Cold Agglutinins* +	—	*Coombs Test* +	—
Acute rheumatic fever	10	0	10	4	6
Lupus erythematosus Acute disseminated type	5	0	5	4	1

Note that the one case of acute disseminated lupus erythematosus, which gave a negative Coombs test, was found to give a positive result with the trypsin test for sensitization.

TABLE III: CONDITIONS AFFECTING THE KIDNEYS

Clinical Diagnosis	*Number Tested*	*Cold Agglutinins* +	—	*Coombs Test* +	—
Acute glomerular nephritis ..	1	0	1	1	0
Subacute nephritis ..	1	0	1	0	1

TABLE IV: CONDITIONS AFFECTING THE RESPIRATORY TRACT

Clinical Diagnosis	*Number Tested*	*Cold Agglutinins* +	—	*Coombs Test* +	—
Atypical pneumonitis	28	4	24	3	25
Subacute pneumonitis	3	0	3	3	0
Virus influenza ..	6	0	6	0	6
Pulmonary tuberculosis	2	2	0	0	2

TABLE V: INFECTIVE DISEASES

Clinical Diagnosis	*Number Tested*	*Cold Agglutinins* +	—	*Coombs Test* +	—
Infective hepatitis .	30	0	30	2	28
Q fever	2	0	2	0	2
Typhoid fever	3	0	3	0	3
Relapsing fever ..	1	0	1	0	1
Syphilis					
Acquired .. .	56			37	19
Congenital	1	0	1	1	0
Trypanosomiasis ..	1	0	1	1	0
Malaria	2	0	2	1	1

It is of great interest that the one case of trypanosomiasis also gave a positive result in the Coombs test. Many years ago it was noted that marked auto-agglutination of red cells and erythrophagocytosis occurred in cases of sleeping sickness. This case had had a full course of treatment with Bayer 205 and had had several injections of Tryparsamide when the blood for the Coombs test was taken. Whether the sensitization of the red cells result from the infection or its treatment therefore remains uncertain.

Of the two cases of malaria tested, one gave a positive result in the Coombs test. This case had also received treatment for two days before the specimen was collected. Obviously the sensitization of red cells in both malaria and trypanosomiasis needs further study.

It is significant that the Coombs test also gave positive results in a large proportion of the cases of acquired haemolytic anaemia, acute rheumatic fever, lupus erythematosus and subacute pneumonitis.

It is now generally accepted that the result of the Coombs test differentiates the acquired form of acholuric jaundice from the congenital form. The finding that one case of aplastic anaemia similarly gave a positive Coombs test raises the question whether some of these cases and also of the analogous cases of agranulocytosis and thrombocytopenia may not also result from the action of immune bodies. Indeed it is likely that some cases of these conditions will be found to have such a basis, although the few cases tested in this series were found to give negative results.

It may also be significant that in one case of glandular fever the Coombs test gave a positive result. Serum of patients with this disease, of course, often give high titres of agglutination with sheep red cells, which is the basis of the Paul-Bunnell test, the accepted diagnostic test in glandular fever. The aetiology of glandular fever still remains undiscovered. It would be worthwhile investigating whether auto-antibodies do not play a role in the pathogenesis of this disease.

The finding that some patients suffering from acute rheumatic fever, acute dermatomyositis, acute disseminated lupus erythematosus, and acute Stevens-Johnson syndrome show sensitization of the red cells also raises the question whether these conditions do not also result from the action of auto-antibodies. Perhaps it should be pointed out first that the demonstration of an auto-antibody in a patient suffering from a particular disease does not necessarily mean that the antibody is responsible for this disease. This is particularly so in cases of lupus erythematosus in which it is often possible to demonstrate antibodies against a variety of different antigens. However, until proved otherwise, the auto-antibodies which have been demonstrated in these conditions will remain under the suspicion of playing some role in their pathogenesis. This suspicion is naturally strengthened by the fact that other lines of evidence, including the results of experimental studies, also tend to incriminate auto-antibodies in the pathogenesis of the collagen diseases. The one case of acute nephritis tested also gave a positive result in the Coombs test.

The three cases of subacute pneumonitis whose sera gave a positive result in the Coombs test all had a similar history. These patients had an acute attack of influenza.

which caused them to stay in bed for several days. However, soon after getting up they complained of not recovering their strength as well as they had expected. All complained of a persistent slight cough and one of them had blood-tinged sputum in the morning. Crepitations were found at the bases of the lungs. This condition of the lungs gradually extended and approximately three months after the initial acute attack of influenza two of these cases experienced increasing difficulty in breathing. They terminated in an acute condition of anoxia. The other case began to improve after three months.

On post-mortem examination, the lungs of the two fatal cases were found to be acutely congested. On microscopic examination marked congestion of the lung capillaries and an extensive exfoliation of the alveolar epithelium was seen. The progression of the anoxic state apparently was due to a decreasing area of functioning respiratory epithelium.

A full account of the clinical and post-mortem findings of these cases will be published separately. For the present it is worth noting that there is such a state of exfoliative pneumonitis and that in these cases the finding of a positive result in the Coombs test suggests that it may have an auto-allergic basis.

DISCUSSION

The significance of these findings presents an intriguing problem. In the case of acquired acholuric jaundice, the demonstration of sensitization of the red cells in conjunction with the other findings, indicates that this condition is caused by an auto-haemolysin. Whether the demonstration of sensitization of red cells in the various other conditions, in which the disease process primarily affects tissues other than red cells, has the same significance is a moot question. However, it is of interest that sensitization of red cells has been shown to occur in some cases of the diseases previously suspected of being auto-allergic or hypersensitivity diseases. These include rheumatic fever and the other collagen diseases. It was thought possible that the sensitization might be broader than the tissue primarily concerned in the development of the auto-allergic state and that, if these were indeed hypersensitivity diseases, the sensitization might include the red cells. This was the main reason for undertaking this study. The results have apparently vindicated this idea and strengthened the suspicion that auto-antibodies are concerned in the pathogenesis of the diseases in which positive results were obtained. However, other possibilities still have to be considered. It has been observed that in most cases of the auto-allergic or hypersensitivity states there is a hyperglobinaemia. Whether this hyperglobinaemia is a result of the development of auto-antibodies, as seems probable, or whether the process of auto-sensitization results from a hyperglobinaemia, due possibly to an endocrine imbalance, is not yet clear. These are vital questions. It may well be that both possibilities are involved. It is well known that only a small proportion of those exposed to sensitizing agents develop sensitivity. This minority presumably has a constitutional tendency to develop sensitivity. Perhaps this tendency depends on an endocrine imbalance. In those having this tendency, the particular tissue or organ which becomes involved in the sensitivity process, in addition to constitutional factors, may depend on the method and duration of the exposure to and on the nature of the sensitizing agents.

The demonstration that a disease results from a hypersensitivity state has now more than academic interest. Recent work has shown clearly that most cases of these conditions can be alleviated, temporarily at least, by the administration of ACTH and Cortisone. The importance of a clear understanding of the pathogenesis of these conditions, and of the correct interpretation of this pathogenesis is thereby emphasized.

The administration of ACTH and Cortisone appears to result in a decrease or sometimes an inhibition of inflammatory reactions. Theoretically, therefore, it would be unwise to advocate their administration in the infective diseases, unless the infection can be controlled by drugs or antibiotics. In some cases, where the infection can be controlled, the use of ACTH or Cortisone may be beneficial. It would be especially beneficial when the reaction to the infection rather than the infection itself is mainly responsible for the ill effects of the illness. This may happen in some cases of pneumonia and pneumonitis where the reaction is so intense that the alveolar epithelium may be cut off from contact with the air and the patient may experience difficulty in getting enough air into his lungs to oxygenate the blood adequately. If the infection in these cases can be controlled by giving the appropriate drug or antibiotic, then the giving of ACTH or Cortisone is indicated.

Theoretically, too, the administration of ACTH and Cortisone is indicated in the tissue hypersensitivity or auto-allergic diseases. In these conditions, as far as can be seen, the tissue reactions serve no useful purpose. Indeed, they are the very basis of the harmful effects of the disease. The inhibition of these tissue reactions would result in the alleviation of the patient's symptoms and signs and also may prevent much tissue damage. It is unfortunate that the tissue hypersensitivity state in many cases tends to persist and to progress and often to end in an acute fulminating condition. In these chronic conditions it has been found necessary to continue the administration of Cortisone or ACTH indefinitely, for when it is stopped the condition may relapse immediately.

In some cases the hypersensitivity state may be temporary. In such cases the administration of ACTH and Cortisone may tide the patient over the dangerous period of hypersensitivity and so prevent tissue damage, which, if not prevented, would ultimately result in a progressive illness. The outstanding example of such a condition is rheumatic fever. The successful prevention of the chronic progressive heart damage resulting from rheumatic fever would, of course, alleviate one of the most serious diseases of childhood. There are many other conditions which are known to be alleviated by the administration of ACTH and Cortisone. The success of this treatment emphasizes the need for a careful re-examination of the pathogenesis of many diseases.

In this investigation a few cases of a variety of diseases were tested for auto-sensitization of red cells. In each disease a much greater number of cases will have to be studied before it is possible to assess the significance of sensitization of red cells. This is now being done systematically and no doubt similar studies are being

carried out in many different institutions throughout the world. Such studies in determining the presence or absence of auto-antibodies in various diseases may help to elucidate the pathogenesis of some of them.

SUMMARY

It has been suggested that auto-antibodies are concerned in the pathogenesis of many diseases. These auto-antibodies develop against various tissues, the cells of which have been made auto-antigenic by being altered by the action of toxins, chemical and physical agents or by the presence of intracellular parasites.

It is difficult to detect auto-antibodies against tissue cells. Auto-antibodies against red cells can be detected directly by determining whether auto-agglutinins or iso-agglutinins are present in the patients' serum or by the application of the Coombs test or other tests for detecting the sensitization of red cells by immune globulin. It was considered possible that auto-antibodies to various tissue cells might involve the red cells as well as the tissue cells primarily affected. Accordingly the blood of patients with various conditions has been systematically tested for sensitization of red cells. It was found that the majority of cases of syphilis gave a positive Coombs test but most cases of other acute and chronic infective diseases gave negative results. Most cases of acquired acholuric jaundice, acute rheumatic fever, acute disseminated lupus erythematosus also gave positive results in the Coombs test. These findings suggest that auto-antibodies may be concerned in the pathogenesis of these diseases. Three cases of subacute pneumonitis, two of which ended fatally, also gave a positive result in the Coombs test. This suggests that this condition, which apparently is a clinical entity not described before, has an auto-allergic basis.

It is noted that the administration of ACTH and Cortisone is probably harmful in infective diseases unless the infection can be controlled by the prior or simultaneous giving of drugs or antibiotics which can control the infection. On the other hand the administration of these hormones is beneficial in the hypersensitivity and auto-allergic diseases. It is therefore important to distinguish clearly between the infective diseases and the hypersensitivity states.

REFERENCES

1. Gear, J. (in the press).
2. Loutit, J. F. and Mollison, P. L. (1946): J. Path. Bact., **58**, 711.
3. Gear, J. (1946): Trans. Roy. Soc. Trop. Med. Hyg., **39**, 301.
4. Morgan, I. M. (1947): J. Exp. Med., **85**, 131.
5. Woods, A. C. (1921): J. Amer. Med. Assoc., **77**, 1317.
6. Smadel, J. E. (1937): J. Exp. Med., **65**, 541.
7. Smadel, J. E. and Farr, L. E. (1939): Amer. J. Path., **15**, 199.
8. Cavelti, P. A. (1947): Arch. Path., **44**, 13.
9. Zoudendyk, A. and Gear, J. H. S. (1950): Brit. Med. J., **2**, 1175.
10. Coombs, R. R. A., Mourant, A. E. and Race, R. R. (1945): Brit. J. Exp. Path., **26**, 255.

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ABSTRACT

Penicillin Treatment of Syphilis. Arthur C. Curtis *et al.* (1951): J. Amer. Med. Assoc., **145**, 1223.

Penicillin has been used for eight years in the treatment of syphilis. The most satisfactory type is the procaine penicillin in oil with 2% aluminium monostearate.

For early syphilis the authors recommend 2,400,000 units on the first day, followed by four injections of 600,000 units at four-day intervals. They obtained a cure rate of 90% with this method. Clinical relapses were seen in 5% of cases.

In late syphilis 6,000,000 units of penicillin gave as good results as those obtained with any previous type of therapy.

In cardiovascular syphilis the value of penicillin has not yet been fully determined.

In neurosyphilis 6,000,000 to 12,000,000 units should be given. This may have to be repeated and malaria therapy given in addition.

In the prevention of congenital syphilis penicillin has been shown to be the most effective drug ever used; 4,800,000 units are advised. Children with congenital syphilis respond well to penicillin in the early stages in doses of 10,000 to 15,000 units per pound of body weight daily for ten days or twice weekly for four weeks. Older children (more than two years) should have 600,000 units daily for ten days or twice a week for five weeks.

Reactions are less frequent with procaine penicillin with aluminium monostearate than with other forms of penicillin. Urticaria and serum sickness like reactions are the commonest. Herxheimer reactions occur mostly in early cases of syphilis.

Penicillin far surpasses any previously used anti-syphilitic remedy.

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EDITORIAL

SLEEPING AND WAKING

Little scientific attention was paid to that third of our lives passed in sleep, until Freud made his discovery that the experiences of childhood recur in symbolic form as dreams. For some time afterwards it seemed that sleep had become the special territory of the psychiatrist. To the Freudian the state of sleep represents a turning away from the real external world [1]; from an analytical standpoint sleep is regarded as a nightly regression associated with a temporary denial of reality.[2] The desire to sleep signifies a life-long instinct to return to an intra-uterine existence.[3]

More recently the experimental physiologists have made determined attempts to understand the sleeping state, and many interesting findings have been reported. The statement that 'during sleep consciousness is lost' [4] is clearly an inadequate definition. An unconscious person is not roused instantaneously by a touch on the arm or the sound of a burglar in the room, nor does he immediately regain possession of his faculties as does a man who is roused from sleep. Sleep is a periodic, complex psychophysical state involving dimming of consciousness with relaxation of the skeletal muscles and temporary changes in the sensory-motor functions.[5]

Animals use the hours of darkness for sleep. Presumably man did so too until he devised the amenities of comfortable shelter, light, warmth and intellectual amusement. The time allocated to sleep has diminished. Contemporary man in many cases suffers the disability of not being able to sleep for even a few hours during the night, and mountains of sedative pills are consumed each year. 'Every man's insomnia is as different from his neighbour's as are his day-time hopes and aspirations. Those seven precious hours of sleep suddenly break in two. There is, if one is lucky, the first sweet sleep of night and the last deep sleep of morning, but between the two appears a sinister, ever-widening interval.'[6]

1. Freud, S. (1933): *New Introductory Lectures on Psychoanalysis*, Chap. 1. London: Hogarth Press.
2. Davison, C. and Delmuth, E. L. (1946): Arch. Neurol. Psychiat., **55**, 364.
3. Freud, S. (1949): *Outline of Psychoanalysis*, Chap. 5. London: Hogarth Press.
4. Brain, W. R. and Strauss, E. B. (1945): *Recent Advances in Neurology and Neuropsychiatry*. 5th ed. London: J. and A. Churchill Ltd.
5. Pai, M. N. (1946): Proc. Roy. Soc. Med., **92**, 756.
6. Fitzgerald, F. Scott (1945): *The Crack-Up*. New York: New Directions.

VAN DIE REDAKSIE

SLAAP EN ONTWAKING

Weinig wetenskaplike aandag was gegee aan daardie één derde van ons leeftyd wat met slaap deurgebring word, totdat Freud sy ontdekking gemaak het dat die ondervindings uit die kinderperiode terugkeer in die simboliese vorm van drome. Vir enige tyd daarna het dit gelyk asof slaap die besondere gebied geword het van die psigiater. Vir die Freudiaan, stel die slaaptoestand voor, 'n afwyking van die werklike uiterlike wêreld;[1] van uit 'n analitiese standpunt beskou, is slaap 'n nagtelike terugval verbonde aan 'n tydelike negering van die werklikheid.[2] Die drang om te slaap dui aan 'n lewenslange natuurlike drang om terug te keer na 'n intra-uterine lewenswyse.[3]

Heel onlangs, het eksperimentele fisioloë vasberade pogings aangewend om die slaaptoestand te begryp en baie interessante bevindinge is gerapporteer. Die bewering, dat ‚bewussyn verlore gaan gedurende die slaapperiode'[4] is duidelik 'n ongenoegsame beskrywing. 'n Bewustelose persoon word nie oombliklik gewek deur 'n stootjie teen die arm of 'n geritsel wat 'n inbreker maak in die kamer nie; ook herwin hy nie dadelik volle beheer oor sy geestesvermoëns, soos iemand wat uit sy slaap opgewek word nie. Slaap is 'n ingewikkelde psigies-fisiese toestand, wat 'n demping van die bewussyn meebring met verslapping van die skeletspiere sowel as verbygaande veranderinge in die sensori-motoriese werksaamhede.[5]

Diere benut die donker ure om in te slaap. Vermoedelik het die mens dieselfde gedoen totdat hy die aangenaamhede uitgedink het vir 'n lekker onderdak, lig, warmte en intellektuele afleiding. Die tyd wat vir slaap afgestaan word het verminder. Die hedendaagse mens ly in baie gevalle aan die tekortkoming van selfs nie vir 'n paar uur in die nag te kan slaap nie sodat berge van kalmerende pille jaarliks verbruik word. ‚Iedere mens se slaaploosheid is netso verskillend van dié van sy buurman syne soos sy daaglikse verwagtings en doelstellings is. Daardie sewe kosbare slaapure breek skielik op in twee. Daar is, as 'n mens gelukkig is, die soete voorslaap, en die diepe, nánag se slaap; maar tussen dié twee in verskyn daar 'n onheilspellende, altyd wyer wordende tydsverloop.'[6]

1. Freud, S. (1933): *New Introductory Lectures on Psychoanalysis*, Hoofstuk 1. Londen: Hogarth Press.
2. Davison, C. en Delmuth, E. L. (1946): Arch. Neurol. Psychiat., **55**, 364.
3. Freud, S. (1949): *Outline of Psychoanalysis*, Hoofstuk 5. Londen: Hogarth Press.
4. Brain, W. R. en Strauss, E. B. (1945): *Recent Advances in Neurology and Neuropsychiatry*. 5de ed. Londen: J. en A. Churchill Beperk.
5. Pai, M. N. (1946): Proc. Roy. Soc. Med., **92**, 756.
6. Fitzgerald, F. Scott (1945): *The Crack-Up*. New York: New Directions.

In the vast majority of cases, insomnia is a manifestation of anxiety and while sedation may afford symptomatic relief, cure can result only if the underlying psychogenic factors are discovered and treated.

Hypnosis is sometimes used to treat hyposomnia, and the hypnotic trance was considered to be a state of deep sleep. Until the advent of the electro-encephalograph there was no reliable method of judging whether a subject was asleep or not. (In deep sleep irregular, large, slow waves, delta waves, are obtained.) The hypnotic trance has been shown to be a state of consciousness unrelated to sleep, for the EEG of a subject in an hypnotic trance does not resemble the sleep pattern but is essentially the same as that obtained during wakefulness.[7]

It is probable that the function of sleep has a localization in the cerebral hemispheres. In the absence of insomnia, it is possible to fall asleep voluntarily and in a reasonably short time. Sleep therefore appears to be under higher cortical control. Le Gros Clark [8] has suggested that the prefrontal cortex is the projection area of the hypothalamus and, from the clinical evidence provided by patients with lesions of the hypothalamus, it appears that the hypothalamic region is the main regulator of the sleep mechanism, the hypothalamus being the centre for wakefulness and damage to it resulting in somnolence. Hess [9] maintains that sleep is an active process produced by stimulation of the hypothalamic area.

The act of sleeping has been studied in many laboratories. There is evidence that satisfactory sleep is dependent on complete physical relaxation. A person who awakens tired in the morning has not experienced adequate muscular relaxation, and as a direct result has undergone mental anxiety and emotional states. McDonnell [10] has prescribed the correct method for lying in bed: 'lateral recumbency with the overlying knee on the mattress and external to the underlying leg'. He contradicts the psychiatrists, insisting that it is not dream imagery which awakens a subject at night, but mechanical causes from incorrect sleep posture.

In an attempt to investigate the changing levels of sleep, Kleitman [11] has measured the movements of the sleeping person. He has constructed an apparatus which measures the total time spent in moving, and found that after the first two hours motility abates and sleep becomes deep. McGlade [12] strapped a crystal microphone over the pyloric sphincter and studied gastric emptying during wakefulness and sleep. During the day the pylorus opened

7. Dynes, J. B. (1947): Arch. Neurol. Psychiat., **57,** 84.
8. Clark, W. E. Le Gros (1948): Lancet, **1,** 353.
9. Hess, W. R. (1944): Helv. Physiol. Pharmacol. Acta., **2,** 137.
10. McDonnell, J. M. (1946): Brit. J. Phys. Med., **9,** 46.
11. Kleitman, N. (1944): *Medical Physics.* Chicago, Illinois: Year Book Publishers, Inc.
12. McGlade, H. B. (1942): Amer. J. Digest. Dis., **9,** 137.

By 'n meerderheid van gevalle, is slaaploosheid 'n teken van bekommernis en, hoewel kalmering (deur middels) 'n simptomatiese verbetering daarin mag meebring, kan genesing alleenlik geskied as die grondoorsaaklike psigiese faktore ontdek en behandel word.

Hipnose word soms aangewend ter behandeling van slaaploosheid en die hipnotiese beswyming was beskou as 'n diepe slaaptoestand. Tot op die koms van die elektro-enkefalograaf, was daar geen betroubare metode waarvolgens beoordeel kon word of iemand aan die slaap was of te nie. (Tydens diepe slaap, word daar groot, onreëlmatige, stadigverlopende deltagolwe verkry.) Die hipnotiese beswyming is egter bewys te wees net maar 'n toestand van die bewussyn, nie verwant aan die slaaptoestand nie, want die EEG van 'n persoon wat onder hipnotiese beswyming verkeer lyk nie op dié van 'n slapende nie, maar is in hoofsaak soos dié wat verkry word gedurende die wakkerperiode.[7]

Dit is waarskynlik dat die funksie van slaap gelokaliseer is in die grootharsings. By afwesigheid van slaaploosheid is dit moontlik om vanself aan slaap te raak binne 'n redelik korte tyd. Dit lyk dus of slaap beheer word deur die hoëre dele van die brein. Le Gros Clark [8] het aan die hand gedoen dat die prefrontale breinkorteks die vooruitgeskuifde area is van die hipotalamus en uit kliniese gegewens, verkry van pasiënte met letsels aan die hipotalamus, wil dit blyk asof die hipotalamusarea die hoof reguleerder is van die slaapmeganisme, sodat die hipotalamus die sentrum is vir die waaktoestand en as dit beskadig word veroorsaak dit slaperigheid. Hess [9] hou vol dat slaap 'n aktiewe proses is wat veroorsaak word deur prikkeling van die hipotalamusarea.

Die slaapakte is al deur baie laboratoria bestudeer geword. Daar is bewyse dat bevredigende slaap afhang van algehele fisiese ontspanning. Die persoon wat moeg wakker word in die môre, het geen genoegsame spierontspanning gehad nie, en as 'n direkte gevolg daarvan, het hy onrustige geestelike en gevoelsomstandighede ondergaan. McDonnell [10] het die regte wyse beskrywe hoe om in die bed te lê: ‚Syligging, met die boonste knie op die matras bo-oor die onderste been.' Hy weerspreek die psigiaters en hou vol dat dit geen droombeeldery is wat 'n persoon snags wakker maak nie, maar wel meganiese oorsake as gevolg van 'n verkeerde liggaamshouding gedurende die slaaptoestand.

Gedurende 'n poging ter ondersoeking na die veranderinge van die slaappeil het Kleitman [11] die bewegings gemeet van 'n slapende. Hy het 'n toestel ontwerp wat die totale tyd meet wat gebruik word met bewegingsmakery en het gevind dat ná die eerste twee uur die bewegings bedaar en slaap dieper word. McGlade [12] het 'n kristal mikrofoon vasgemaak oor die sluitspier van die pilorus, daarmee het hy die ontlediging van die maag by die wakende en die slapende toestand bestudeer. By dag het die pilorus stilweg oopgegaan wanneer halfver-

7. Dynes, J. B. (1947): Arch. Neurol. Psychiat., **57,** 84.
8. Clark, W. E. Le Gros (1948): Lancet, **1,** 353.
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quietly as partly digested food passed into the duodenum, and the sounds grew fainter as the stomach emptied. When the subject fell asleep with food in his stomach, however, the pyloric sphincter opened with a sharp snap and the food passed rapidly with a rumbling sound. McGlade found that, in those given to such nocturnal activities, twitchings of the feet were almost synchronous with the noise of the relaxing sphincter. He concludes, perhaps hastily, that whether or not a dream will be experienced depends on the kind of food in the stomach at the time of going to bed.

It has been said that man is at his lowest ebb in the early hours of the morning. The heart rate is at its slowest during the second half of the night, and the body temperature is at its lowest level during the middle of the sleep period. The urine output is decreased during sleep and the blood diluted.

While investigations proceed, innumerable people with insomnia wait anxiously for the mysteries of sleep to be made plain, and content themselves with sedative tablets. Balinese medicine-men have a manoeuvre for inducing sleep; pressure is applied to the sides of the neck over the carotid sinuses, and before the patient becomes unconscious he experiences visual disturbances and a choking sensation.[13] The use of this dangerous treatment for excitable patients who do not respond to orthodox sedation has also been reported from India. It is unlikely that medical practitioners in occidental civilized communities will resort to such manoeuvres.

13. Schlager, E. and Meier, T. (1947): Acta Trop., **4**, 127.

teerde voedsel na die duodenum gegaan het en die geluide het dowwer geword namate die maag hom ontledig het. Waar die persoon egter aan slaap geraak het met kos in die maag, het die pilorus-sluitspier met 'n skerp geluid geopen terwyl die voedsel vinnig deurgegaan het met rommelende geluid. McGlade het gevind dat by hulle wat snags woelig was, was die rukkings van die voete feitlik gelyktydig met die geraas van die ontsluitende sluitspier. Hy maak die ietwat haastige gevolgtrekking dat, of daar gedroom sal word of nie, dáárvan afhang welke soort voedsel daar by slaaptyd in die maag aanwesig is.

Daar is al beweer dat 'n mens se toestand op sy laagste is ten tyde van die vroeë môre-ure. Die spoed van die hartklop is minste gedurende die tweede helfte van die nag terwyl ook die liggaamstemperatuur laagste is teen die middel van die slaapperiode. Die urieneafskeiding verminder gedurende die slaap en die bloed word verdun.

Terwyl ondersoeke aan die gang is, wag daar angsvallig ontelbare mense wat aan slaaploosheid ly op die verklaring van die geheime van slaap en bevredig hulself met kalmerende tablette. Balinese toordokters het 'n kunsbehandling waardeur slaap aangebring word: druk word uitgeoefen alkante van die nek, reg op die sinus carotici en vóór die pasiënt sy bewussyn verloor ondervind hy gesigstoornisse en wurgsensasies.[13] Die aanwending van hierdie gevaarlike behandeling in die geval van prikkelbare pasiënte wat nie gevolg gee aan die gewone kalmeringsmiddels nie, is ook van uit Indië vermeld. Dis egter onwaarskynlik dat medici in die beskaafde samelewings in die weste tot sulke maatreëls hul toevlug sal neem.

13. Schlager, E. en Meier, T. (1947): Acta. Trop., **4**, 127.

MEDITERRANEAN ANAEMIA

AN INVESTIGATION OF NINETEEN CASES IN A SINGLE FAMILY

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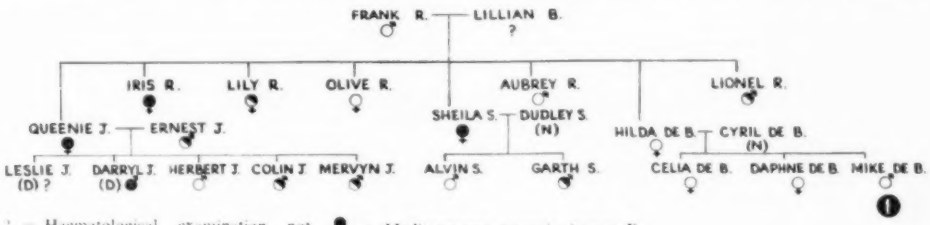
The term Cooley's anaemia (thalassaemia, Mediterranean target cell anaemia) was originally restricted to a fatal hypochromic anaemia in young children, usually of Mediterranean descent, with target cells and normoblasts in the peripheral blood. However, a less severe form in adults has been reported by Wintrobe,[1] Dameshek [2] and others, and its hereditary basis has become established.

This investigation involves 19 cases in a family over three generations (Fig. 1). The trait was transmitted by two individuals, viz. Frank R. (born in St. Helena, the



? = Haematological examination not done.
D = Died in early childhood.
N = Normal blood picture.
● = Mediterranean anaemia (group I).
◔ = Mediterranean anaemia (group II).
○ = Mediterranean anaemia (group III).

Fig. 1. Family Tree in 19 Cases of Mediterranean Anaemia.

TABLE I. HAEMATOLOGICAL DATA IN A FAMILY WITH MEDITERRANEAN ANAEMIA

	GROUP I				GROUP II						GROUP III								
Name	*Darryl J.*	*Queenie J.*	*Iris R.*	*Sheila S.*	*Ernest J.*	*Colin J.*	*Mervyn J.*	*Lily R.*	*Lionel R.*	*Gavin S.*	*Alvin S.*	*Herbert J.*	*Frank R.*	*Olive R.*	*Aubrey R.*	*Hilda de B.*	*Celia de B.*	*Mike de B.*	*Daphne de B.*
Age (years)	5	27	29	23	32	7	4	21	19	4/12	4	2	62	14	17	26	8	3	5
Haemoglobin (gm. %)	6·3	8·2	7·8	8·2	13·3	10·7	9·0	11·4	13·3	8·8	9·6	10·7	15·5	13·6	14·0	11·8	11·8	11·8	12·8
Red Cells (millions per cu. mm.)	3·01	3·64	4·35	3·90	6·40	6·41	5·44	6·25	7·01	3·59	4·30	4·73	5·86	5·10	4·98	4·82	4·53	4·19	5·0
C.I.	0·66	0·72	0·57	0·68	0·67	0·53	0·52	0·58	0·61	0·64	0·73	0·72	0·87	0·88	0·91	0·80	0·83	0·90	0·82
P.C.V. (%)	24	32·5	28·5	31	46	37	32	40	46·5	30	32	32	48·5	43	43·5	39	37	34	40·5
M.C.H.C. (%)	26	25	27	26	29	29	28	28·5	29	29	30	33·5	32	31·5	32	30	32	34·5	31·5
M.C.V. (cu. μ)	80	90	66	79	72	58	60	64	67	83	74	70	82	84	87	81	83	81	81
M.C.H. ($\mu\mu$g)	21	23	18	21	21	17	17	18	19	24	22·5	24	26·5	27	28	24·5	26	28	26
M.C.D. (μ^3)	?	8·9	8·0	9·0	7·4	6·8	7·0	7·2	7·2	7·2	7·3	7·1	7·3	7·4	7·2	7·2	6·7	7·2	7·0
M.C.A.T. (μ)	?	1·44	1·31	1·24	1·59	1·60	1·56	1·57	1·65	2·04	1·77	1·73	1·96	1·87	2·13	1·99	2·30	1·99	2·10
Smear[1]																			
Target Cells	+ + +	+ + +	+ + +	+ + +	+ + +	+ +	+ + +	+ + +	+ + +	+ + +	+ +	+ +	+ + +	+	+ + +	+ +	+	+	+
Hypochromia	+ + +	+ + +	+ + +	+ + +	+ +	+	+ +	+ + +	+ +	+	—	—	—	—	—	—	—	—	—
Anisocytosis and poikilocytosis	+ +	+ +	+ +	+ +	+	+	+	+	+	—	+	—	—	—	—	—	—	—	—
Reticulocytes (%)	4·5	23·0	6·0	5·1	0·8	1·2	0·7	1·4	1·3	0·6	1·1	0·6	1·4	?	?	2·1	0·4	0·3	1·1
Normoblasts (per 100 white cells)	23	329	3	330	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Serum Bilirubin (mg. per 100 c.c.)	1·85	1·65	2·50	2·20	0·55	0·54	0·61	0·55	0·54	0·56	?	0·55	0·50	0·69	0·44	0·81	0·56	0·50	0·49
Fragility[2]																			
Commenced (%NaCl)	0·34	0·36	0·40	0·42	0·40	0·36	0·40	0·40	0·40	0·40	0·30	0·40	0·40	0·40	0·40	0·32	0·40	0·32	0·40
Completed (%NaCl)	0·22	0·04	0·08	0·10	0·08	0·12	0·16	0·16	0·16	0·04	0·04	0·04	0·16	0·16	0·16	0·12	0·20	0·20	0·16

1. Measurements by halometry.
2. + + + (marked), + + (moderate), + (slight), — (absent).
3. Control fragility tests: Haemolysis commenced at between 0·44% to 0·40% NaCl and was complete at 0·32% to 0·28% NaCl.

population of which is of somewhat mixed racial origin) and Ernest J. (born in South Africa of English parentage).

Frank R. married a coloured South African who died in cardiac failure before this investigation was started. Apart from a normal haemoglobin level (14.5 gm. %) details of her blood picture were not available.

From the haematological and clinical view-points the cases fall clearly into three groups (Table I).

Group I: Cases showing the characteristic anaemia with evidence of excessive blood destruction and regeneration.
Group II: Cases showing the characteristic anaemia only.
Group III: Cases showing only evidence of the trait.

GROUP I

This includes four cases.

History. The common complaint is of a general lassitude and dyspnoea on exertion. This was most marked in the case of Darryl J., who was a classical case of childhood Cooley's anaemia.

All three females in this group have chronic ulceration over the medial or lateral malleolus (Fig. 2). The ulcers occasionally heal up but following minor trauma soon break down again. Skin grafting and X-ray therapy has had only a temporary beneficial effect. The ulcers first appeared at the ages of 14-16 years and in one case (Iris R.) have been present for 15 years.

A third significant complaint (Queenie J.) is that of severe post-partum haemorrhage with each of five pregnancies, necessitating transfusions.

The sclera is persistently jaundiced and the urine is dark. From time to time (at intervals of a few weeks) the jaundice becomes more intense and this lasts for a day or two. These episodes are associated with increased lassitude.

Physical Findings. Typical mongoloid features are present in two of the four cases (Darryl J. and Iris R.). The spleen was easily palpable in three of the four cases and was just palpable in the fourth (Iris R.). In the case of Darryl J. the liver was slightly enlarged (two fingers). He had a systolic thrill at the apex and a systolic murmur

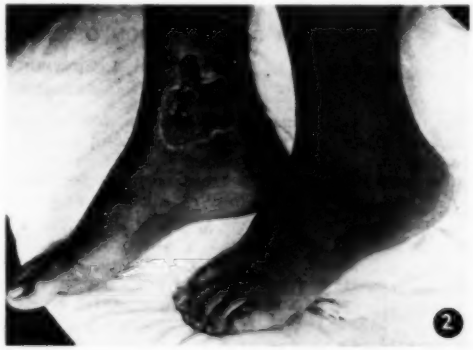


Fig. 2. Chronic ulceration in a case of Mediterranean anaemia.

at all areas of the heart. The icterus and the chronic ulcers have been described.

Haematological Findings. Details of the blood picture are presented in Table I. The essential feature is a

haemoglobin value of about 8.0 gm. % or less with a low colour index and M.C.H.C.

The smear shows large thin hypochromic target cells with some anisocytosis, poikilocytosis and stippling. Normoblasts were present in all cases in the peripheral blood before splenectomy and varied from over 100 normoblasts per 100 white cells in the case of Darryl J., to 2-3 normoblasts per 100 white cells in the case of the others.

Total white counts were between 12,000 to 14,000 per c.mm. with a normal differential count. Platelets were present in normal numbers.

Evidence of increased destruction and regeneration of red cells is provided by the persistent icterus with a raised serum bilirubin (1.65 to 2.5 mg. per 100 c.c.), a positive indirect van den Bergh reaction, and the persistently raised reticulocyte count.

As in all the cases to be described, the red cells show an increased resistance to saline haemolysis.

The bone marrow shows a marked erythroid hyperplasia, normoblasts constituting 50-80% of the nucleated cells present (Table 2).

There was no response to numerous courses of iron therapy given over the last few years. Coombs test (developing antibodies) was negative. There was no evidence of sickling.

The urine contained urobilinogen in increased amount. Porphyrins were not detected.

Radiological Findings. Definite radiological changes were present in all the cases in this group. In the case of Darryl J. they were the classical radiological changes of a Cooley's anaemia. In the case of the others there was medullary expansion with coarse irregular bone trabeculation in the long bones, ilia and vertebrae. Amorphous opacities were present in the shafts of the metacarpals and proximal phalanges.

Effects of Splenectomy. A splenectomy was performed on two of the four patients in this group (Queenie J. in 1946; Sheila S. in 1947). Both showed the usual striking rise in the numbers of normoblasts in the peripheral blood following the operation. The number has varied from 300 normoblasts per 100 white cells to as high as 1,600. Counts of over 800 normoblasts per 100 white cells have been recorded in both patients on a number of occasions. Otherwise the patients have not benefited in any way from the splenectomy.

GROUP II

Six cases fall into this group. All were perfectly fit and physical examination was negative.

Haematological Findings. The haemoglobin level is either within normal limits or slightly below normal (9-13 gm. %), but the striking feature is the high red cell count which is often over 6 million per c.mm. (Table 1). The colour index and M.C.H.C. is again low.

The smears show numerous hypochromic target cells but unlike group I, the cells on the whole appeared normocytic. Anisocytosis and poikilocytosis were present but not marked.

Both serum bilirubin and reticulocyte counts were within normal limits.

The bone marrow in one case showed a moderate erythroid hyperplasia, normoblasts constituting 29% of the nucleated cells (Table 2).

Radiological changes were not demonstrable.

TABLE 2: BONE MARROW DATA IN A FAMILY WITH MEDITERRANEAN ANAEMIA

	Normal	*Group I*				*Group II*		*Group III*		
		Darryl J.	*Queenie J.*	*Iris R.*	*Sheila S.*	*Lily R.*	*Garth S.*	*Aubrey R.*	*Olive R.*	*Frank R.*
Haemocytoblast	0·0—1·0	0·0	0·0	0·0	0·0	0·8	0·6	0·0	0·0	0·0
Myeloid Series:										
Polymorphs:										
Neutrophil	9·0—34·0	6·5	21·8	9·5	22·0	25·6	16·2	33·2	35·2	34·0
Eosinophil	0·5—3·0	1·5	1·4	0·0	2·0	1·0	0·4	2·0	2·2	3·4
Basophil	0·0—0·5	0·0	0·0	1·0	0·0	0·0	0·0	0·2	0·0	0·0
Metamyelocyte:										
Neutrophil	5·0—18·0	2·0	5·2	6·0	3·5	14·8	6·2	12·2	15·0	18·0
Eosinophil	0·0—2·5	0·0	0·4	0·0	0·0	0·6	0·4	1·2	1·2	0·8
Basophil	—	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Myelocyte:										
Neutrophil	2·0—20·0	4·5	7·6	8·0	7·5	11·0	9·2	13·0	9·8	10·8
Eosinophil	0·3—2·0	0·5	1·2	0·0	1·0	1·4	0·8	1·0	2·2	1·6
Basophil	0·0—0·5	0·5	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Promyelocyte	0·5—10·0	2·5	0·4	2·0	0·0	0·4	4·2	1·2	1·0	1·4
Myeloblast	0·2—4·0	0·0	0·4	3·0	0·0	0·4	2·0	0·2	1·0	0·4
Erythroid Series:										
Proerythroblast	0·0—2·0	2·5	10·8	0·5	2·0	0·0	0·6	0·0	0·8	1·0
Normoblast:										
Basophilic	0·3—3·0	15·5	5·4	9·5	} 59·0	2·2	1·2	1·2	1·0	1·2
Polychromic	5·0—15·0	47·0	} 36·0	39·0		25·0	7·6	9·8	7·4	14·8
Orthochromic	1·0—7·0	9·0		15·0		2·0	3·6	2·0	1·2	2·8
Lymphocyte	2·5—24·0	8·0	8·4	6·0	3·0	14·6	44·2	20·0	23·8	9·6
Plasma Cell	0·0—2·0	0·0	0·8	0·0	0·0	0·2	0·2	2·6	0·0	0·0
Megakaryocyte	0·0—2·0	0·0	0·0	0·0	0·0	0·0	0·6	0·0	0·0	0·2
Myeloid—Erythroid Ratio	3·4—1	0·25—1	0·67—1	0·45—1	0·6—1	1·9—1	3—1	4·9—1	6·3—1	3·6—1

GROUP III

This group comprises the remaining nine members of the family. They have two findings in common:

1. Red Cells show an increased resistance to saline haemolysis.
2. The presence of target cells in the peripheral blood.

The smears showed no evidence of hypochromia and the M.C.H.C. was normal. The bone marrow was normal. Indefinite radiological changes were present in the case of Olive R., otherwise radiological changes were absent.

In some of the cases in this group a slightly increased resistance to saline haemolysis was the only real abnormality and in the absence of a family history they would probably be accepted as normal.

DISCUSSION: SOME ASPECTS OF THE PATHOGENESIS

The Nature of the Fundamental Defect. There have been various suggestions about the nature of the fundamental defect in Mediterranean anaemia. These range from external factors similar to favism,[3] an infective organism,[4] a defect of the type existing in pernicious anaemia,[5] to a defect in the utilization of iron.[6]

The most acceptable view is that of a congenital defect in haemopoiesis whereby an erythrocyte deficient in haemoglobin is produced. This can arise in a number of ways:

1. A red cell is produced which is generally deficient in intracellular material. Such a cell would obviously be able to hold a correspondingly lesser quantity of haemoglobin.
2. There is a defective utilization of iron in the synthesis of haemoglobin.

The concept of a red cell deficient in intracellular stroma arose from the behaviour of these cells in hypotonic saline. It was held that these cells had a normal outer membrane but a lesser amount of internal material and hence were able to take up an excessive amount of fluid before disrupting. If this view is correct, there is no need to postulate a defective haemoglobin synthesis in order to explain the hypochromia. The work of Walsh *et al.*[7] suggests that iron is initially attached to acceptors in the red cell stroma and thus a cell with a lesser amount of stroma will only be able to hold a correspondingly lesser amount of iron and hence of haemoglobin. If this is correct, the cell is fully saturated with haemoglobin and there is no hypochromia in the usually accepted sense.

On the other hand, the work of Haden [8] strongly suggests that the behaviour of the red cell in hypotonic saline depends on its shape and as the cell changes towards a globular shape the resistance of the cell to hypotonic solutions decreases in almost direct proportion. It is clear from Table I that in this condition the cells are definitely flattened with normal or increased diameters and diminished thickness. On the basis of Haden's work one would anticipate that such cells would show an increased resistance to saline haemolysis and no further explanation of this phenomenon is required.

It is thus probable that an abnormally thin cell is the major morphological characteristic of the erythrocyte in Mediterranean anaemia. Whether in addition there is a deficient amount of intracellular stroma, in the present state of our knowledge remains mere surmise.

The viewpoint that there is a defective utilization of iron in the synthesis of haemoglobin has received fairly wide acceptance. The concept has been carried further and it has been suggested that it is part of a general defect in the utilization of iron. The evidence in support of this view has been the general siderosis observed at autopsy and this has been likened to the appearance of the tissues in haemochromatosis.[9]

It is clear, however, that this iron deposition may be a consequence of any haemolytic anaemia. It is also found in any case receiving numerous transfusions,[9] and as the type of case coming to autopsy is invariably the severe classical Cooley's anaemia which has probably received a number of transfusions and is generally jaundiced, the significance of the siderosis remains doubtful.

More recently Sisson *et al.*[10] have found an elevated serum iron level and saturation of the iron-carrying globulin fraction of the plasma in cases of Mediterranean anaemia. Again this cannot be interpreted as indicating a primary defect in iron metabolism. A high serum iron is common to all conditions where haemoglobin synthesis is depressed, e.g. pernicious anaemia, pyridoxine deficiency and hypoplastic anaemia,[11] as well as conditions with excessive iron storage, e.g. haemochromatosis.

Thus there is probably a defective haemoglobin synthesis in this condition. Whether it involves a defective utilization of iron is at present uncertain. It is associated with the production of an abnormally thin red cell.

The Haemolytic Tendency. The importance of the haemolytic element in the pathogenesis of Mediterranean anaemia has not received sufficient recognition. In the more severe cases of this disease (group I) there is a persistent and at times a well-marked icterus from which the patient is never free. There is also a fairly clear-cut correlation between the degree of morphological abnormality of the red cells and the presence of icterus. In these cases the red cell consists merely of a large outer ring with a small elevation in the middle and there is convincing evidence that these abnormal cells are more susceptible to the normal haemolytic mechanisms.

Thus Kaplan and Zuelzer [12] investigated the survival time of erythrocytes from cases of frank Mediterranean anaemia transfused into normal subjects. The half-life of these cells was 25 days as compared with the half-life of 62 days obtained for normal cells.

On the other hand, the survival time of normal red cells transfused into patients with severe Mediterranean anaemia was normal. Thus it is clear from their work that the haemolytic element is due to defects in the erythrocyte and not to any abnormal haemolytic mechanism.

The survival time of erythrocytes from patients exhibiting the milder forms of Mediterranean anaemia was also tested and was found to be normal. Thus where the defect in the erythrocyte is of a lesser grade (group II), the tendency to increased red cell destruction is far less and although each red cell carries an abnormally low quota of haemoglobin, by virtue of a high red cell count (6-7 million per c.mm.) these patients are able to maintain an adequate haemoglobin level. The red cells here are hypochromic target cells but are normal in diameter, the M.C.V. being slightly low.

Where only the 'target cell trait' is present, the patients appear normal in all respects and, indeed, unless the condition is particularly looked for, it is liable to be missed.

Microcytosis was inferred from the low M.C.V. rather than from inspection of the smears in this series, and poikilocytosis and anisocytosis, though present, were not as prominent a feature in these less severe cases as is sometimes stated in the literature.

The marked normoblastic marrow hyperplasia seen in the more severe cases (group I) is thus attributable to at least two factors:

1. The more important is probably excessive red cell destruction.
2. It is also an attempt to compensate for the low quota of haemoglobin carried by the individual red cell: and where excessive red cell destruction is minimal (as in Group II) a high red cell count is maintained successfully.

NOMENCLATURE

It has been customary to distinguish between the severe, usually fatal childhood cases of Cooley's anaemia (sometimes termed thalassaemia major) and those of lesser severity in older subjects (thalassaemia minor). This classification that has evolved with our knowledge of the disease since the severe cases were known many years before the more benign ones were described. It does not, however, give a fair reflection of the clinical, haematological and radiological picture in this disease. Thus all the severer cases (group I) have a similar blood picture including erythroblastosis, all are icteric, have an enlarged spleen and show radiological changes. It is, therefore, not unreasonable to extend the term thalassaemia major to include all these and the following classification is suggested:

Group I: Cases showing well-marked hypochromia, splenomegaly, icterus, marked normoblastic marrow hyperplasia and radiological changes (thalassaemia major).

Group II: Cases showing marked hypochromia, but no icterus and often high red cell counts (thalassaemia minor).

Group III: Cases showing minimal or no evidence of hypochromia and no icterus (thalassaemia trait), but in common with the cases in Groups I and II they show an increased resistance to saline haemolysis, the presence of target cells in the peripheral blood and the familial incidence.

TRANSMISSION OF THE TRAIT

It has been variously suggested that the target cell trait is transmitted both as a mendelian dominant and as a recessive, and that the severe form occurs in homozygous individuals inheriting the trait from both parents. In this family, at least, the trait appears to be a mendelian dominant. The possibility of a homozygous condition was present in four cases, viz. the children of Queenie J. and Ernest J. Of these, one (Darryl J.) was a classical Cooley's anaemia (group I), two others fell clearly into group II (Colin J. and Mervyn J.), and the fourth showed a milder form and was put into group III.

ERYTHROBLASTOSIS

Perhaps the most striking haematological feature of Mediterranean anaemia is the remarkable erythroblastosis present in the more severe cases, or which follows a splenectomy. It is far greater in degree that can be attributed to the stress on the bone marrow of a severe anaemia. In recent years evidence has accumulated that the spleen plays some part in the maturation of the erythron and in the release of the red cells from the marrow to the peripheral blood.

Thus Jacobson [13] made the observation that shielding the spleen during irradiation of animals in some way promoted subsequent bone marrow recovery.

McFadzean and Davis [14] observed a large increase of siderocytes (red cells with granules giving a positive prussian blue reaction) in the peripheral blood following splenectomy in acquired haemolytic jaundice. Before splenectomy the bone marrow contained large numbers of normoblasts with siderotic granules. It has been suggested that removal of the nucleus in the normoblast is within the sphere of splenic influence.[15]

The response to splenectomy in this condition must strengthen the view that the spleen plays an important function in the control of erythropoiesis, but the precise manner in which it functions is at present obscure.

SUMMARY

Nineteen cases of Mediterranean anaemia in a single family are described. On clinical, haematological and radiological grounds they fall clearly into three groups:

Group I: Cases showing well-marked hypochromia, icterus, spenomegaly, normoblasts in the peripheral blood, and an elevated reticulocyte count. The bone marrow showed marked normoblastic hyperplasia, and radiological changes were present. The females in this group showed chronic ulceration over the malleoli.

Group II: Cases showing hypochromia, either low or normal haemoglobin values, but usually high red cell counts (6-7 million cells per c.mm.), and no icterus. The bone marrow may show a moderate degree of normoblastic hyperplasia.

Group III: Cases showing evidence of the trait, viz. the red cells have an increased resistance to saline haemolysis. Target cells are present in the peripheral blood.

The pathogenesis of the condition is discussed.

I wish to thank Dr. H. R. Holmes, M.D., D.M.R.E. (Lond.), M.R.C.P. (Lond.) for reporting on the X-ray appearances in this series.

REFERENCES

1. Wintrobe, M. M. *et. al.* (1940): J. Amer. Med. Assoc., **114,** 1530.
2. Dameshek, W. (1940): Amer. J. Med. Sci., **200,** 445.
3. Schieber, C. L. (1945): Lancet, **2,** 851.
4. Fawdry, A. L. (1944): Lancet, **1,** 171.
5. Whipple, G. H. and Bradford, W. L. (1932): Amer. J. Dis. Child., **44,** 336.
6. Wintrobe, M. M. (1946): *Clinical Haematology*. Philadelphia: Lee and Febiger.
7. Walsh, R. J. *et al.* (1949): Science, **110,** 396.
8. Haden, R. L. (1934): Amer. J. Med. Sci., **188,** 441.
9. Schwartz, S. O. and Blumenthal, S. A. (1948): Blood, **3,** 617.
10. Sisson, T. R. et. al. (1950): Proc. Soc. Exper. Biol. Med., **74,** 258.
11. Granick, S. (1949): Bulletin N. Y. Acad. Med., **25,** 403.
12. Kaplan, E. and Zuelzer, W. W. (1950): J. Lab. Clin. Med., **36,** 511.
13. Jacobson (1950): Quoted in the 1950 *Year Book of Medicine*, Chicago: The Year Book Publishers, Inc.
14. McFadzean, A. J. S. and Davis, L. J. (1947): Glasgow Med. J., **28,** 237.
15. Best and Taylor (1950): *The Physiological Basis of Medical Practice*. London: Baillière, Tindall and Cox.

BILHARZIASIS IN THE TRANSVAAL*

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Bilharziasis has been described in the Northern and Eastern Transvaal since this area was first settled by Europeans in the latter part of the nineteenth century. This fertile region was long laid waste and rendered unsuitable for agricultural development by the ravages of malaria which overshadowed the more subtle menace of bilharziasis, although we now know that this latter disease covers a much larger tract of country than malaria ever did.

It is common knowledge to-day that following on many years of research into the bionomics of the malaria vector mosquitoes and five years of intensive control, malaria has ceased to be of economic importance throughout the 60,000 square miles of the Northern and Eastern Transvaal. Agrarian development has taken place on a hitherto unknown scale in these formerly malaria-ridden regions.

Throughout all these years the staff of this Department attached to the Malaria Unit have often encountered cases of bilharziasis and Bilharzia snails. Some have actually contracted bilharziasis and the Unit from the time of its inception was always fully aware of the scourge of Bilharzia. Table E reflects the results of urine examinations of several thousand of Native children done as early as 1937. This work was done by the field inspectorate of this Unit at a time when little or no attention was being paid to the schistosomiasis problem by the public or other official bodies.

There are three main ways by which the incidence of bilharziasis in a community may be reduced:

1. Destruction of the intermediate host—the snail.
2. Education and propaganda work aimed at the prevention of water pollution and the reduction of exposure to infection.
3. Destruction of the Bilharzia worms in the definitive host—man—by a mass treatment campaign.

Jopling,[1] basing his opinion largely on the relative failure of Mozley's[2] work in Southern Rhodesia, as reported by Blair,[3] argues that the accepted methods of snail destruction are of little value and that prior attention should be paid to education and propaganda work coupled with the provision of basic sanitary needs.

Amongst our rural Native population which comprises the bulk of the problem, propaganda and education work has yielded disappointing results as it involves a complete departure from the Native's customary mode of life. The Native draws his water from Bilharzia-infected waters, the herd boys swim there, and the Native women wash themselves, their babies and their clothing there. Very few Natives in infected areas can therefore escape being infected with bilharziasis some time in their life.

The provision of alternative clean water supplies—even for domestic purposes—would be a very costly undertaking and is at present impracticable in our rural areas.

With regard to Europeans many of the aforementioned difficulties do not exist and others have been removed by progressive planning such as the provision of swimming baths at European schools. The valuable work of the Transvaal Bilharzia Committee which was established in the early 1930's should be mentioned in this regard. In spite of this an appreciable number of Europeans still contract bilharziasis each year.

A mobile unit of the Transvaal Bilharzia Committee has since its inception established treatment camps at various European schools, with gratifying immediate results, but experience has taught us that patients more often than not obtain fresh infections within a short time. This tendency is even more noticeable when follow-up examinations are done on Native school children who have been treated by the Departmental District Surgeon staff and reported as cured.

Any attempt with the drugs available to treat and cure our rural Native population of bilharziasis faster than they can become infected, must inevitably fail and we agree with Shousha[4] that treatment alone as a method of Bilharzia control, is of very little value.

That bilharziasis cannot be controlled by propaganda and treatment is quite clear to-day, but there is one gratifying factor which emerges from the years of propaganda and treatment . . . the public is rapidly becoming Bilharzia minded. The value of the changeover from almost open hostility towards the problem to open co-operation can never be overstressed.

It is apparent that we have no alternative but to engage in battle against the snail host of Bilharzia, though this does not mean that propaganda and treatment are valueless. Indeed, as a complementary measure they are of great value, and this work must continue.

RESEARCH

(a) *Distribution of Molluscan Hosts.* As a primary step in the campaign against the disease it was essential to study the habits and incidence of the various snail hosts of *B. haematobium* and *B. mansoni* and such work was commenced in the Transvaal in 1948-1949.

Despite difficulties caused by the absence of an established system of snail systematics for this country, and our inability in the field to determine definitely whether the cercariae shed by the various snails were those of *B. haematobium*, *B. mansoni*, or other schistosomes, our staff in the Northern Transvaal embarked upon an energetic study of the incidence and favourite habitats of our various important fresh-water snails, namely *Physopsis africana*, *Bulinus tropicus*, *Planorbus pfeifferi*, *Limnae*

* The References will be published at the end of the concluding part of this paper.

natalensis and *Pyrgophysa forskalii*. (With regard to snail systematics, we are inclined to agree with Schwetz [5] that the classification of snail vectors tends to be much too artificial.)

During the past two years a comprehensive programme of survey work was undertaken. The tables below reflect the findings to date in regard to the distribution, or frequency of occurrence, of the various potential hosts in different types of habitat. The zones delimited in the map (Fig. 1) and Tables are:

i. Zoutpansberg—Letaba.
ii. Pietersburg—Lydenburg.
iii. Potgietersrust — Waterberg — Rustenburg — Marico — Pretoria—Bronkhorstspruit—Groblersdal.
iv. Barberton—Nelspruit—Pilgrim's Rest.

Table B expresses the percentage incidence of these various fresh-water snails from all the habitats searched in the calendar year 1950.

Table C expresses the distribution of Physopsis and Planorbis in the various habitats as percentage of their respective total numbers.

Table D also reflects the number of Physopsis and Planorbis but now expressed as percentage of the total number of snails collected in each particular habitat.

It will be noted that Physopsis snails were found in all the types of water examined but this important snail shows a definite predilection for streams, canals and other water sources with a heavy plant growth.

With the exception of cement dams, Planorbis snails

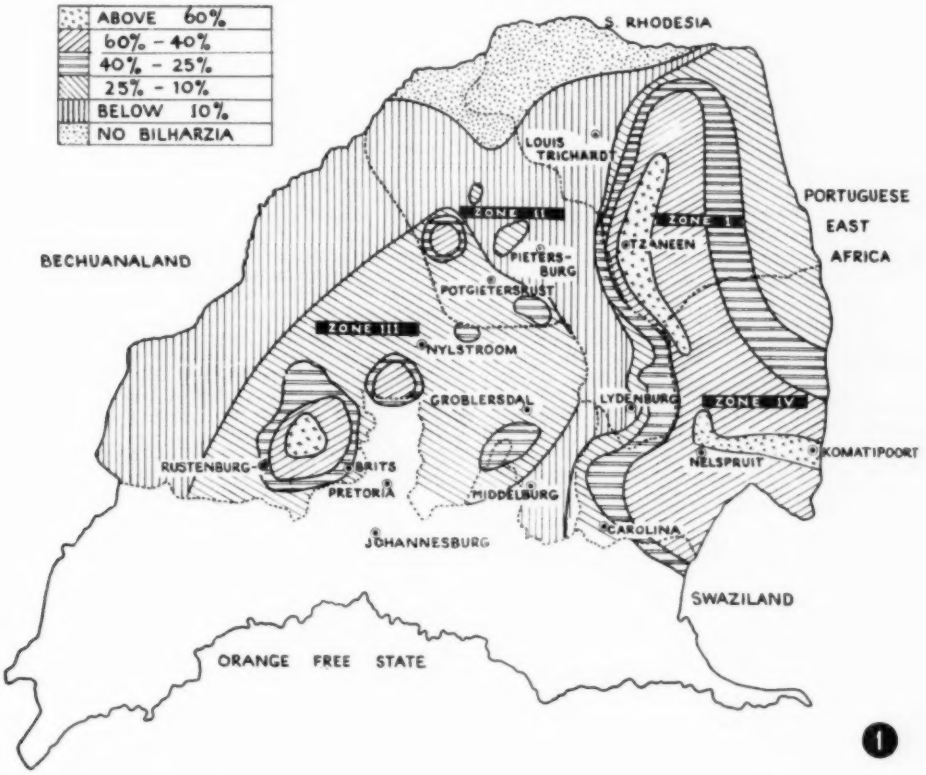

Table A reflects (on a quarterly basis) the actual numbers of *all* fresh water snails collected in the four zones during the calendar year 1950. Within limits, it may be stated that approximately the same number of man-days were spent in searching for these snails, in each quarter of the year.

seem to show a definite preference for running water as opposed to standing waters.

There appear to be no marked peaks with regard to the number of snails found throughout the year with the possible exception of Pyrgophysa, which occurs in relatively small numbers at the beginning of the summer

TABLE A: TOTAL NUMBER OF FRESH-WATER SNAILS COLLECTED IN TRANSVAAL IN 1950

1950 *Zones*	I					II					III					IV				
	PH	L	B	P	PL	PH	L	B	P	PL	PH	L	B	P	PL	PH	L	B	P	PL
First Quarter	20	53	—	—	75	855	7533	3301	—	1108	518	594	422	—	541	1278	7673	—	146	1709
Second Quarter	1645	5118	684	114	1265	1737	8251	7200	—	1588	1286	1546	1241	—	921	1286	1546	1241	—	921
Third Quarter	1874	1395	2953	287	825	1118	10631	3591	15	2256	749	1722	1308	—	250	1285	8180	—	164	1458
Fourth Quarter	107	1498	69	15	498	1128	12266	2748	83	5142	1106	4044	1461	—	464	1350	—	30	75	1466
Total	3646	8064	3706	416	2663	4838	38681	16840	98	10094	3659	7906	4432	—	2176	5172	17399	1271	385	5554

Totals for Four Zones:

Physopsis	17,315 (PH)
Limnaea	72,050 (L)
Planorbis	20,487 (PL)
Bulinus	26,249 (B)
Pyrgophysa	899 (P)
	137,000

TABLE B: PERCENTAGE INCIDENCE OF VARIOUS FRESH-WATER SNAILS COLLECTED IN TRANSVAAL IN 1950

1950	*Physopsis*	*Limnaea*	*Bulinus*	*Pyrgophysa*	*Planorbis*
First Quarter	10·3	61·4	14·3	0·6	13·4
Second Quarter	14·6	51·2	20·4	0·4	13·4
Third Quarter	12·3	54·8	19·7	1·2	12·0
Fourth Quarter	12·2	59·2	14·1	0·4	14·1

(fourth quarter). This, of course, applies to the general picture, and not to the findings of any one given area, where appreciable fluctuations may, and do, occur.

When we consider the topographical distribution of the various snails we will notice that Bulinus is chiefly found in Zones II and III which constitute the high-lying and relatively more arid areas of the Northern Transvaal where, incidentally, the lowest incidence of bilharziasis is found. Physopsis on the other hand, though distributed throughout all areas is found in larger numbers in the lower, wetter regions (our Zones I and IV) where bilharziasis is at its worst.

There is no doubt in our mind that even if our *Bulinus tropicus* can transmit *B. haematobium* as stated by Porter[6] its role as a vector is unimportant. We, like

TABLE C: DISTRIBUTION OF PHYSOPSIS AND PLANORBIS IN THE VARIOUS HABITATS EXPRESSED AS PERCENTAGES OF THEIR RESPECTIVE TOTAL NUMBERS

1950

Breeding Places	*First Quarter*		*Second Quarter*		*Third Quarter*		*Fourth Quarter*	
	Physopsis	*Planorbis*	*Physopsis*	*Planorbis*	*Physopsis*	*Planorbis*	*Physopsis*	*Planorbis*
Cement dams	10·3	44·7	7·7	41·9	4·5	16·0	13·2	40·0
Pans and other open standing waters	5·6	11·5	15·6	5·3	13·0	15·1	15·1	14·1
Running waters with grass and lilies	37·8	20·7	23·4	16·5	36·2	33·1	50·0	25·9
Grass pans	9·8	0·3	17·6	2·1	27·2	17·3	15·2	9·9
Streams, canals and water sources with much plant growth	36·5	22·8	35·7	34·2	19·1	18·5	6·5	10·1

TABLE D: NUMBERS OF PHYSOPSIS AND PLANORBIS EXPRESSED AS PERCENTAGES OF THE TOTAL NUMBER OF SNAILS COLLECTED IN VARIOUS HABITATS

1950

Breeding Places	*First Quarter*		*Second Quarter*		*Third Quarter*		*Fourth Quarter*	
	Physopsis	*Planorbis*	*Physopsis*	*Planorbis*	*Physopsis*	*Planorbis*	*Physopsis*	*Planorbis*
Cement dams	3·06	13·0	4·4	22	2·5	9	4	14
Pans and other open standing waters	9·9	25	17·2	6	9	10	25	34
Running waters with grass and lilies	10·8	7	11·4	7	15	13	25	20
Streams, canals and water sources with much plant growth ..	27·5	22	25·4	23	21	20	12	22
Grass pans	10	1	20·98	2	18	11	11	11

de Meillon,[7] Blair[3] and Barlow[5] *et al.*, have neither found infected *Bulinus tropicus*, nor been able to infect them. Incidentally, the same holds for *Lymnaea natalensis* and *Pyrgophysa forskallii* which have also been stated to be vectors, but which we, like de Meillon[7] (for *Lymnaea natalensis*) and Gillet[9] (for both) have neither found infected, nor been able to infect. *Physopsis africana* is a very definite vector, and the early work of Becker[10] in this regard, has been confirmed by many subsequent investigators.

It should be noted that this work is continuing on the same scale, and within five years it should be possible to be much more definite.

(b) *Molluscicides.* In recent years a large number of possible molluscicides have been tested and reported on, but none appear to be ideal. Khalil and Halawani[11] tried Cloreben but this was too toxic to fish. Da Mota[12] tried benzene-hexachloride but found that a concentration of 100 parts/million was needed—we have confirmed this work with BHC and obtained similar results with Gamma-BHC and its various isomers. McMullen and Graham[13] found that DDT was of no practical value—we also confirmed this work. Nolan and Berry,[14] and Nolan, Berry and Gonzalez[15] investigated a series of organic compounds which were tested against *Australorbis glabratus* in concentrations of 10 parts per million, and report good results with (*inter alia*) sodium penta-chlorophenate and copper penta-chlorophenate, although the latter was somewhat toxic against guppies, catfish and eels. Other chemicals which have been tested include copper quanylurea, calcium arsenate, calcium cyanimide, Paris green, dinitro-ortho-cyclohexyl-phenol (McMullen and Graham) and 'inferior' lime (Luttermosen[16]) but all have one or other disadvantage.

Our only really encouraging results under field conditions were obtained with the well-known copper sulphate, but much experimental work was required to determine the optimum concentrations necessary to destroy fresh-water snails in the various types of breeding places without harming other desirable forms of water life or making the water dangerous for animals or plants.

We soon found that copper sulphate concentrations of 0.6 to one part per million were sufficient to destroy all snails in standing water such as dams where the volume could fairly readily be assessed. In running water with a variable flow, however, it is by no means easy to establish and maintain control since it is not only practically impossible to calculate the volume of water to be treated, but alterations in the flow rapidly change the concentration of copper sulphate from point to point. Under these latter conditions we found that (estimated) concentrations of 10 to 20 parts per million, or even more, were needed to obtain satisfactory control.

It should be appreciated that these concentrations are calculated in terms of the $CuSO_4$ added (i.e. immediate concentration) and do not express the concentration of molluscicidal Copper in the water, which decreases rapidly due to various chemical and physical reactions with organic and particulate inorganic matter in the water. A biological experiment showing this reduction in molluscicidal effect gave the following results:

Healthy snails were exposed to river water which had been collected at varying intervals after a spraying with one p.p.m. of $CuSO_4$ and their survival time was noted.

Water to Which Snails were Added	*Percentage Left Alive* 15 *mins.*	30 *mins.*	1 *hour*	3 *hours*	6 *hours*	12 *hours*	24 *hours*
(*a*) Riverwater before treatment	100	100	100	100	100	100	100
(*b*) Riverwater collected immediately after application of $CuSO_4$ ..	0	0	0	0	0	0	0
(*c*) As for (*b*) but the snails were removed to fresh water after 1 minute ..	50	23	7	3	0	0	0
(*d*) Riverwater collected ½ hour after application of $CuSO_4$ ..	77	73	53	7	0	0	0
(*e*) Riverwater collected 1 hour after application of $CuSO_4$ ..	97	97	83	47	40	33	13

Abdel Azim and Barlow[5] have also shown that a Copper Sulphate concentration of 30 parts per million falls to 1/10 within four hours.

Bearing all this in mind, our present control method is as follows:

After an initial application of 5 to 10 p.p.m. careful weekly observations are carried out to determine when new snails appear. We attempt to destroy all the snails in the water with the first application, thus preventing the deposition of fresh spawn. Only spawn already deposited can produce the new snail population. When snails reappear and not within 14 days from the first application, a second application is made—also 5 to 10 p.p.m. It may take, depending on favourable or adverse climatic conditions, a month or more before the first of the new snail batch appears. It is realized that to apply further $CuSO_4$ before *all* the spawn is hatched is a waste of material, because the $CuSO_4$ concentration does not destroy the spawn (a very high concentration is needed for this). If more snails should occur after the second application, then a third and fourth application are made, but it has rarely been necessary to treat any water more than three times, if such waters are not re-infected from other sources. The copper sulphate is usually sprayed on the water surface with a knapsack-type sprayer (as used for our malaria work) though other methods have been tried.

This whole procedure may be repeated two or three times a year. It should be remembered that it is unusual under our conditions for snails younger than three months to produce spawn (in fact it has never occurred in our experiments) and it is therefore unnecessary to start another course of treatment within this period.

It must be stressed that utmost care is essential when treating water with $CuSO_4$ for snail destruction. No water must be left over and it is equally purposeless to treat a portion of a stream or valley or even to treat one stream and leave out others in the vicinity, although not directly connected. Re-infestation with snails has invariably occurred from the untreated sources. Blocks of country—with natural barriers, mountains for instance, should be tackled and not small bits and pieces, because in this way no lasting results can ever be obtained. This important proviso should be borne in mind when localized control (i.e. control limited to areas of high actual or potential risk) rather than country-wide molluscicidal control is attempted, as was suggested by Blair[3] as a possible programme for Southern Rhodesia.

In the same way it is useless to start upstream and hope that the copper sulphate will be carried down. This unstable chemical is rapidly destroyed even after a few yards as is shown in the following experiment:

Copper sulphate was added to an earth dam and water samples tested from various points at differing times:

Water Samples Taken	*Concentration of Copper in p.p.m.*
(*a*) From the dam before adding $CuSO_4$ ..	0·23
(*b*) From the dam immediately after adding $CuSO_4$	19·5
(*c*) From the dam 17 hours after adding $CuSO_4$	3·12
(*d*) From 20 ft. below the dam (outlet furrow) at same time as (*c*)	0·78
(*e*) From 120 ft. below dam (outlet furrow) at same time as (*c*) and (*d*)	0·39
(*f*) From 220 ft. below the dam (outlet furrow) at same time as (*c*), (*d*) and (*e*) ..	0·39

$CuSO_4$ even in a weak concentration is most lethal to snails—but due to the high absorption rate in water it is difficult to maintain even such a weak concentration. A most interesting controlled experiment in which an attempt was made to obtain a concentration of one p.p.m. $CuSO_4$ in slowly running waters yielded the following results:

Treated/Untreated		*Percentage Alive of Snails Caught*				
		Before Treatment	*One Week Later*	*One Month Later*	*Three Months Later*	*One Year*
Treated Stream	A	79%	0%	3%	3%	95%
Treated	B	97%	0%	0%	1%	99%
Untreated	C	94%	98%	100%	100%	99%
Untreated	D	95%	100%	100%	100%	60%

This experiment was carried out over five miles of river and over 6,000 snails (dead or alive) were examined.

This bears out that snails can under certain circumstances at least, be controlled with one p.p.m. $CuSO_4$, even in slowly running water. On the other hand, 10-20 p.p.m. or more may be necessary to do this under different conditions and on a larger scale.

It must be appreciated that $CuSO_4$ is very far from being an ideal molluscicide as it is unstable and not nearly as selective in its action as would be desirable, but we agree with da Mota that it still remains the most effective molluscicide (within economic limits) which we have available.

Before going further we would like to point out two important features of this work. Firstly, we have not yet undertaken control work as such. The areas we have treated with copper sulphate were each picked as being representative of one particular set of conditions and as being suitable for the limited field research our material permitted. Secondly, our immediate aim has not been to eradicate the snail vector in our experimental areas, but has been to reduce the snail populance to below the transmission-density—a most important economic consideration if bilharzia control is to be extended on a country-wide basis.

(To be concluded)

QUESTIONS ANSWERED

Treatment of Pyelitis

Q. What is the best chemotherapeutic agent to use in a proved case of *B. coli* pyelitis of more than 10 years' duration, without complications?

I understand that *B. coli* becomes streptomycin-resistant after about 20 generations. A 'radical cure' is desired.

A. When the history or clinical examination suggests calculus, hydronephrosis or other abnormality routine pyelography and cystoscopy are carried out, but some workers prefer to do this in every case of urinary tract infection whatever the history or response to treatment.

When sulphonamides are being used treatment is generally effective within five to seven days, and treatment is rarely

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necessary beyond 10 days. Sulphamezathine, for example, has been found to be very effective. In resistant infection treatment with Succinylsulphathiazole or Phthalylsulphathiazole is recommended by some authorities to reduce a source of infection in the large intestine. The urine output should be maintained at 1,000 to 1,500 ml. daily.

Aureomycin, Chloramphenicol, and Terramycin are effective against the common invaders of the urinary tract, but *P. vulgaris* and *Ps. pyocyanea* are resistant; Aureomycin acts best in an acid urine.

If the above-mentioned drugs have not been effective therapy with Calcium Mandelate may be tried. The urine must be rendered highly acid.

Streptomycin, which has to be given by injection, acts best if the urine is rendered alkaline. Because the organisms tend to become resistant rather rapidly, and because of possible toxic effects, it should rarely be given for more than seven days. A definite therapeutic effect should be observed within 48 hours if treatment is going to be successful.

In certain individuals the infection recurs despite expert care and the apparent absence of any demonstrable obstruction. It may be of value to tell female patients to wipe the anus from before backwards after passing a stool to prevent soiling the vulva. Care is also required in wiping the vulva after urination. This is especially important in the last five months of pregnancy.

IN MEMORIAM

DR. MAX GREENBERG

The Southern Transvaal Branch mourns the passing of Max Greenberg, one of our best-loved and keenest members.

Max Greenberg was born in Lithuania on 27 December 1886 and arrived in South Africa, with his family, in 1899 when they settled in Kimberley. He always said that the fact that he took the part of a 'medicine man' in a play at school when he was six years old influenced his choice of a profession. He qualified at Edinburgh in 1910, having graduated in the scheduled time, though he played as hard as he worked. He was interested in football, riding, dancing, skating and, particularly, rowing, for which he received his rowing blue.

After taking his F.R.C.S. at Edinburgh in 1913 he returned to South Africa and took part in the 1914–1918 war, seeing active service in South West Africa.

For a short while after being demobilized he acted as assistant to the late A. H. Watt, in Germiston, and then was appointed honorary surgeon at the Pretoria Hospital and railway surgeon in Pretoria.

In 1923 he became consulting surgeon to the South African Railways in Johannesburg, and soon after was appointed honorary surgical registrar of the Johannesburg General Hospital. The 'General' became one of his main interests, and he devoted a large part of his time to it, becoming eventually senior surgeon to the Transvaal Memorial Hospital for Children, and serving on the Hospital Board for many years.

He was Secretary of the Witwatersrand Branch of the British Medical Association for many years. In 1927 he was elected secretary of the Witwatersrand Branch of the Medical Association of South Africa, and was also responsible for a very successful Medical Congress held in Johannesburg. In addition, he served on the Federal Council.

In 1935 he represented the Medical Association of South Africa at the Medical Congress in Britain, and also the Congress in Australia.

He was elected representative of the Southern Transvaal Branch on the Johannesburg Hospital Board for three years after the promulgation of the 1946 Ordinance.

During the second world war he was not accepted for full-time military service, although he volunteered immediately war broke out; but did valuable work in a part-time capacity, with the rank of Lieut.-Colonel, as surgeon for military patients at the General Hospital and in Pretoria. His pay was £25 per month, which he promptly gave to charities.

He was a connoisseur of art and had one of the finest collections of paintings in South Africa, from which he gave several valuable examples of Africana to the City of Johannesburg in 1948 and 1950. On numerous occasions he assisted struggling artists financially and one of his outstanding characteristics was his impulsive generosity. He was blunt and outspoken and by no means placid in temperament, but he never did a mean or underhand action, although his bluntness sometimes got him into difficulties.

His passing leaves a gap which it will be difficult to fill.

R. B.

PASSING EVENTS

MEDICAL LIBRARY, MOWBRAY

The list of accessions to the Medical Library for April-June 1951 is now ready. Copies will be sent to Members of the Medical Association upon application to the Medical Library, Medical School, Mowbray, C.P.

* * * *

The attention of Members of the Medical Association is once more drawn to the fact that this Medical Library is **open on** Mondays and Thursdays from 8 p.m.-10 p.m. for an experimental period of six months.

* * * *

Dr. L. R. McQuillan has moved to rooms in Bible House, Greenmarket Square, Cape Town. Telephone: 2-7319.

SETTLEMENT SCHEMES

Dr. Friedman, Chief Director of Medical Services of the High Commission Territories accompanied by the Medical Directors of Swaziland and Basutoland will be visiting the FOSA Settlement outside Durban with a view to adopting a similar plan for the Territories.

Mr. Sykes, Vice-Chairman of S.A.N.T.A. and founder of the Settlement scheme in the Union has been in contact with Dr. Friedman and outlined this scheme. Should it meet with their approbation it is proposed to start a pilot settlement scheme for each of the Territories. These will probably be launched by the British Red Cross Society in each territory with the help of the Colonial Office.

OBSTETRICAL AND GYNAECOLOGICAL CONGRESS: CAPE TOWN

The Cape Town branch of the South African Society of Obstetricians and Gynaecologists has arranged a Congress from 3-5 April 1952. The Organizing Committee is as follows: Dr. Lance Impey—*Chairman*; Dr. T. St. Vincent Buss—*Secretary*; *Committee*: Drs. Ruby Sharp, D. Friedlander and P. Massey.

Further details will be announced later.

CAPE TOWN PAEDIATRIC GROUP

A meeting will be held in the Lecture Theatre, Fourth Floor, Groote Schuur Hospital, on Monday, 24 September 1951, at 8.15 p.m.

Dr. Fred Petersen will speak on *Post-nasal Space and its Relation to Aural and Pulmonary Infection*. All practitioners are welcome.

THE BENEVOLENT FUND

Donations from payments made by the Transvaal Provincial Administration in respect of Honoraria:

Previously ackowledged	£6.118	3	2
Dr. N. E. C. de la Hunt	146	19	2
Dr. A. B. Rossouw	10	0	0
Dr. C. Pienaar	10	0	0
Dr. L. Friedlander	46	13	4
Dr. D. Judes	46	13	4

Dr. T. Schneider	115	0	0
Dr. D. Gold	25	0	0
Dr. Ian Macgregor	8	0	0
	£6,526	9	0

The following contributions to the Benevolent Fund during July 1951 are gratefully acknowledged:

Votive Cards: In Memory of:

Dr. C. J. Lyons *by* Dr. C. H. Houghton.
Dr. J. M. Beyers *by* Dr. G. T. van der Vyver.
Mrs. Peter Gordon *by* Dr. and Mrs. L. Impey.
Dr. C. Rowland *by* Dr. Stanley Batchelor.
Mr. Max Greenberg *by* Drs. Cox and Feldman, The Casualty Officers of the Transvaal Memorial Hospital for Children, Dr. I. J. Zadikoff.
Dr. W. P. R. Swemmer *by* Dr. R. Schaffer.
Dr. Ivor Gardiner *by* Border Branch Members, Dr. E. G. van Hoogstraten.
Dr. Barclay *by* Dr. E. G. van Hoogstraten.

Total Amount Received from Votive Cards:	23	18	0

Services Rendered to:

A Retired Colleague *by* Dr. J. S. du Toit.
Mrs. D. Jacob *by* Dr. J. Black.
Dr. J. M. Sachar *by* Dr. J. Prisman.

Total Amount Received from Services Rendered:	3	17	0

Donations:

Dr. W. Welchman, for sale of 'Acute Head Injuries'	1	1	9
Cape Western Branch Members Collection Box	2	18	4
The National Medical Aid Society of S.A.		10	6
Dr. J. K. Langenegger		10	6
Dr. A. H. Sader		10	6
Dr. B. J. Brewitt		10	6
Dr. A. F. Stewart		7	0
Dr. E. F. W. Moon		5	0
Dr. P. H. Kampfraath		5	0
Dr. A. Glatt	2	0	0
Dr. J. S. M. Sililo		10	6
Dr. O. O. Midgley		5	0
Dr. N. R. Butcher		10	6
Dr. A. le Roux van der Merwe		10	6
Dr. R. H. Johnson		10	6
Dr. C. L. Lauf		10	6
Dr. S. H. Kaplan		10	0
	£40	1	7

BOOK REVIEW

A GUIDE TO INCOME TAX RETURNS

A Guide to the Completion of an Income Tax Return of (a) an Individual (b) a Company. By David Shrand, A.S.A.A., C.A. (S.A.). (Pp. 103. 10s. 6d.) Cape Town and Johannesburg: Juta and Company, Limited. 1951.

Contents: 1. The Completion of an Income Tax Return of an Individual. Procedure Relating to Objections and Appeals. 2. The Completion of an Income Tax Return of a Company. Procedure Relating to Objections and Appeals. Appendixes.

Medical practitioners share with other citizens an increasing mystification and irritation about the complicated forms which must be returned now-a-days to the Receiver of Revenue for an income tax assessment.

The *Journal* has recently published a special article devoted to this problem from the doctor's point of view. Mr. Shrand's monograph, however, may also be found of great interest and, in addition, it contains tables of taxation applicable to persons in the various Provinces.

The doctor who wishes to become a student of these affairs will find this Guide a useful investment for a very modest fee.

CORRESPONDENCE

SIR CHARLES HASTINGS CLINICAL PRIZE ESSAY COMPETITION

To the Editor: The *Sir Charles Hastings Clinical Prize Essay Competition* is established by the Association for the promotion of systematic observation, research, and record in general practice. The competition has been extended by the addition of a second prize known as the *Charles Oliver Hawthorne Clinical Prize*. The following are the regulations governing the awards:

1. The *Sir Charles Hastings Clinical Prize*, consisting of a certificate and 50 guineas, will be awarded for the best essay submitted.

2. The *Charles Oliver Hawthorne Clinical Prize*, consisting of a certificate and a sum of money slightly less than the amount of the *Sir Charles Hastings Clinical Prize*, will be awarded for the second best essay submitted.

3. Any member of the Association who is engaged in general practice is eligible to compete for these prizes.

4. The work submitted must include personal observations and experiences collected by the candidate in general practice, and a high order of excellence will be required. If no essay entered is of sufficient merit no award will be made. Candidates in their entries should confine their attention to their own observations in practice rather than to comments on previously published work on the subject, though reference to current literature should not be omitted when it bears directly on their results, their interpretations, and their conclusions. It is suggested that essays should consist of from 3,000 to 10,000 words.

5. Essays, or whatever form the candidate desires his work to take, must be sent to the Secretary, British Medical Association, B.M.A. House, Tavistock Square, London, W.C.1, not later than 31 December, 1951.

6. A study or essay that has been published in the medical press or elsewhere will not be considered eligible for a prize, and a contribution offered in one year cannot be accepted in any subsequent year unless it includes evidence of further work. A prizewinner in any year is not eligible for an award of either of the prizes in any subsequent year.

7. If any question arises in reference to the eligibility of the candidate or the admissibility of his or her essay the decision of the Council on any such point shall be final.

8. Preliminary notice of entry for this competition is required, on a form of application to be obtained from the Secretary.

9. Each essay must be typewritten or printed and must be accompanied by a sealed envelope, enclosing the candidate's name and address, firmly affixed to the essay.

10. The writer of an essay to whom a prize is awarded may, on the initiative of Science Committee, be required to prepare a paper on the subject for publication in the *British Medical Journal* or for presentation to the appropriate Section of the Annual Meeting of the Association.

11. Inquiries relative to the prize should be addressed to the Secretary.

A. Macrae,
Secretary.

British Medical Association House,
Tavistock Square,
London, W.C.1.
June 1951.

NPH 50 INSULIN

To the Editor: As we also received a supply of *NPH 50 Insulin* from The Eli Lilly Co. your article by Schneider and Ehrenstein (14 July) was of great interest to us.

We used our supply mainly in the Diabetic Out-Patient Clinic of the Groote Schuur Hospital. As the new insulin

seemed suitable for patients taking globin insulin or a mixture of protamine zinc and plain insulin, we turned our attention chiefly to patients already under treatment with one of these. Four were mild cases (less than 40 units a day) five were intermediate (40-80 units) and two were severe (60-90 units with danger of ketosis). In assessing the results we paid attention especially to control of glycosuria, the level of the blood sugar, freedom from insulin reactions and the general feelings of the patients.

In one severe case the change from 90 units of a 2:1 mixture (plain : protamine zinc) to 90 units of NPH was followed by an attack of ketosis; this may have had some other cause but we did not feel justified in repeating the treatment with NPH as an out-patient. The other severe case, a newly discovered diabetic, improved more on 68 units of NPH than on the same dose of a mixture of globin; he finally lost his glycosuria on NPH. Improvement of tolerance in a newly discovered diabetes under treatment was certainly occurring, but by alternating the treatments we were convinced that NPH suited him best.

In four mild cases we found less liability to insulin reactions or less glycosuria and a lower range of blood sugar than before. One of the moderately severe cases had considerably more glycosuria than on an equal dose of globin, but two others have shown less glycosuria without reactions. One with Kimmelstiel-Wilson nephropathy, who had taken 100 units of protamine zinc at home, was poorly controlled in hospital on a mixture of 30 plain and 30 protamine; on 60 NPH there was no improvement but on 60 NPH and 15 plain she became almost sugar-free without reactions.

The last patient was an experienced diabetic with a long history whose diabetes was under moderate control but complicated by many hypoglycaemic episodes. On 28 plain and 20 protamine zinc his urine test was green in the morning and yellow or red for the rest of the day; after a few days on 48 units of NPH the tests improved to green with a fair number of blues. He was still liable to reactions but they were less severe. On a reduced dose he became free without heavy glycosuria. His blood sugar was followed on two days with this striking result.

Time	*Plain-Protamine Mixture Blood Sugar (mg. per 100 c.c.) 23 January 1951*	*NPH 50 Blood Sugar (mg. per 100 c.c.) 15 February 1951*
8.30 a.m.	195	153
9.30 a.m.	270	289
11.00 a.m.	380W	207
12.30 p.m.	330	82
2.00 p.m.	380W	142
3.30 p.m.	345	103
4.30 p.m.	341	110

The patients were almost unanimous in stating that they felt better on NPH and there was no doubt that many minor and some major hypoglycaemic symptoms were obviated. They knew, however, that they were getting special treatment and it is well known how encouraging it is to use a new remedy before its charm wears off. We feel sure that some of the improvement was genuine.

This insulin appears to fill several gaps. It is useful when a single dose of protamine or globin is not giving an entirely satisfactory result. It is more useful when a mixture of insulins was needed. The trouble and uncertainty of using two insulin bottles and the need for care not to contaminate the stock of one insulin with the other, have made mixing an unsatisfactory proceeding with all but a few very reliable patients. If there is need for an additional quick-acting effect, plain insulin can be added to NPH and a small addition of ordinary insulin will be effective in the presence of a much larger amount of NPH. This is because NPH is a definite compound and not a mixture of protamine and insulin as is protamine zinc insulin; plain insulin added to NPH therefore remains free and retains its full speed of action. The mixture of NPH and plain insulin should for the same reason have a more predictable effect.

We should like to thank the Lilly Co. for the opportunity of trying this new preparation.

G. C. Linder, W. P. U. Jackson and I. Grayce.

University of Cape Town and
Groote Schuur Hospital,
Observatory, C.P.
7 August 1951.

POST-MORTEM DISSECTION ARTEFACTS OF THE NECK THEIR DIFFERENTIATION FROM ANTE-MORTEM BRUISES

To the Editor: We thank Professor Mackintosh for drawing our attention to certain references in the German literature relating to this subject. The terms of his letter published in the *Journal* of 14 July 1951, suggest that he is under the impression that we claimed to have made an original communication on this subject. That we made no such claim is shown by our reference to the paper by Hocking. The main purpose of our paper was to draw attention to a subject of importance to which no direct reference is made in several standard works on Forensic Medicine in the English language, such as the books by Taylor, Moritz, Smith and Glaister.

I. Prinsloo and I. Gordon.

Durban.
7 August 1951.

W.H.O. AND VENEREAL DISEASE CONTROL

To the Editor: The activities of W.H.O. during 1950 in the control of syphilis and other treponematoses deserve universal commendation. There can be no question that the availability of Penicillin in absorption-delaying vehicles has made it possible for W.H.O. to use a form of treatment that is efficacious, non-toxic and so readily given as to be administratively feasible for mass application. The effectiveness of this form of therapy has been amply demonstrated in the great reduction in the incidence of syphilis that has followed its use in the control campaigns conducted in a number of European countries like Poland, Finland, and Yugoslavia. In India, too, the results of this new form of therapy have been most gratifying. The W.H.O. venereal disease demonstration team has been able to show that high quality work in venereal disease control can be conducted in the poverty-stricken rural areas of India with a minimum of supplies and equipment. Subsequent surveys of the areas covered by the team have indicated a remarkable reduction in the number of new infections. The excellent results achieved in India have induced other countries like Afghanistan, Burma, Ceylon, and Indonesia to send specialists to attend the W.H.O. training courses in advanced clinical syphilology and serology. Simla is at the present time the most important W.H.O. training centre.

Large scale projects in the control of the treponematosis were initiated during 1950 in Haiti, Indonesia, Iraq, and Thailand, and according to a W.H.O. estimate, some 300,000 persons were treated during the year. Similar control programmes are about to be put into operation in the Dominican Republic and the Philippines. In European countries like Bulgaria, Czechoslovakia, Finland, Poland, and Yugoslavia, venereal disease control campaigns have been conducted under the technical supervision of W.H.O. and with supplies furnished by UNICEF; in Italy and Greece W.H.O. directed special attention to the suppression of prenatal and congenital syphilis and also carried out clinical and laboratory demonstrations on Penicillin therapy and the use of cardiolipin antigens for serodiagnosis in several university medical centres in Europe and the Eastern Mediterranean region. The establishment in the United States of America of the International Treponematosis Laboratory Centre (in the School of Hygiene and Public Health of the Johns Hopkins University,

Baltimore) was without a doubt the most notable achievement of W.H.O. during the past year. At this Centre, basic research studies on the biology of the various treponematoses are being conducted with the co-operation of field teams; and an indication of the high quality of the researches undertaken is the recently developed treponema-immobilizing test which has made possible the elucidation of fundamental problems in immunity and serological response to therapy. One might also refer to the important activities of W.H.O. in a special field of serodiagnosis. For several years the organization has been engaged in collecting information with a view to ascertaining which of the many serological tests have gained widest acceptance throughout the world. According to a recent report, the exchange of serum specimens for test performance, evaluation and standardization, arranged in former years between national laboratories in Bulgaria, Denmark, Ethiopia, Finland, Italy and the United Kingdom, has now been extended to laboratories in France, Israel, Norway and the United States of America. Most commendable, too, are the plans which have been made for laboratory training centres in Brazil and Venezuela, and at these centres a demonstration of the step-by-step production of cardiolipin antigen was staged by an expert consultant, seconded by the Statens Seruminstitut in Copenhagen, which has been selected as a W.H.O. Serological Reference Laboratory. The W.H.O. Sub-Committee on Serology and Laboratory Aspects is the body responsible for the organization of these activities.

W.H.O. has, furthermore, organized machinery for the exchange of scientific information regarding recent advances in the control of venereal diseases, and this objective is being achieved by the preparation of technical reports and articles, and by the distribution of relevant literature and technical data on clinical, laboratory and public health aspects of venereal disease control in answer to requests of national health administrations. The W.H.O. Expert Committee on Venereal Infections, having regard to the high incidence of venereal disease among merchant seamen, has been pressing strongly for high priority to be given to the establishment of venereal disease control demonstration projects in the major ports of the world. It is more than likely that the first model port-demonstration project will be set up in Rotterdam, and the view has been expressed that the training-courses which will be offered and the study groups which will be formed will make an important contribution to the reduction of venereal disease incidence among seafarers. In furtherance of its campaign in this direction W.H.O. has prepared an 'International List of Venereal Disease Treatment Centres at Ports'; has prepared a revised individual treatment booklet for the use of seafarers; and has also completed a survey of the serological laboratory facilities of the ports along the Rhine river. The valuable information already collected by W.H.O. has been placed at the disposal of the International Anti-Venereal Disease Commission of the Rhine which met in the Netherlands in 1950. W.H.O. has recently addressed itself to the question of revising the 1924 Brussels Agreement relating to the treatment of venereal disease among merchant seamen.

The W.H.O. Expert Committee on Venereal Infections and Treponematoses found it impracticable to meet during 1950 on account of the Congress of the International Union against Venereal Diseases which took place in Zurich in the same year.

An idea of the results achieved by W.H.O. in the field of venereal disease control may be obtained from numerous publications which have been launched under its auspices. A selected list is presented hereunder in the belief that they will be of assistance to students and general practitioners, etc.:

1. Bekierkunst, A. and Milgrom, F. *Compelment fixation reactions with cardiolipin antigen compared with Kahn reactions.* Bull. World Hlth. Org., 1950, **2**, 687-688.
2. *Cardiolipin Antigens* (WHO/VD/10, October 1950).
3. Coutts, W. E. *Lymphogranuloma Venereum: A General Review.* Bull. World Hlth. Org., 1950, **2**, 545-562.
4. Coutts, W. E., Degos, R., Hellestrom, S., Hermans, E. H., McElligott, G. L. M., Mahoney, J. F., Nagi, I. H. and Rajam, R. V. *Minimum Penicillin Therapy in the Treatment of Treponemal Infections by WHO/UNICEF Field Teams* (WHO/VD, **72**, December 1950).
5. Cutler, J. C. *Survey of Venereal Diseases in Afghanistan.* (2) Bull. World Org. 1950, **2**, 689-703.
6. *Expert Committee on Venereal Infections. Report on the Third Session.* (2) World Hlth. Ord. Techn. Rep. Serol., 1950, **13**.
7. *Expert Committee on Venereal Infections: Sub-Committee on Serology and Laboratory Aspects. Report on the First Session* (2) World. Hlth. Org. Techn. Rep. Serol., 1950, **14**.
8. *Expert Committee on Venereal Infections and Treponematoses: Sub-Committee on Serology and Laboratory Aspects. Report on the Second Session.* (3) (WHO/VD, **73**, November 1950.)
9. *Information on Early Sero-Laboratory Conferences* (WHO/VD/SEROL., **2**, August 1950, and WHO/VD/SEROL., **2**, Add. 1 and Add. 2, September 1950).
10. *International Serodiagnostic-Laboratory Conference: Report on Preliminary Survey* (WHO/VD/SEROL., **4**, August 1950).
11. *International Symposium on Syphilis: Section I. Early Syphilis* (WHO/VD, **67**, October 1950).
12. *International Symposium on Syphilis: Section II. Prenatal and Infantile Syphilis* (WHO/VD, **68**, October 1950).
13. *International Symposium on Syphilis: Section III. Neurosyphilis* (WHO/VD, **69**, October 1950).
14. *International Symposium on Syphilis: Section IV. Serology in Syphilis* (WHO/VD, **70**, October 1950).
15. *Laboratory Activities in a Serologic Testing Phase of the WHO Programme* (WHO/VD/SEROL., **3**, August 1950 and WHO/VD/SEROL., **3**, Add. 1, September 1950).
16. *Preliminary Report on Serologic Methods in the World Laboratories in Member States and Their Serological Methods* (WHO/VD/SEROL., **7**, August 1950 and WHO/VD/SEROL., **7**, Add. 1, September 1950).
17. *Preliminary Serological Report of the WHO Venereal-Disease Demonstration Team*, Simla (India) (WHO/VD/SEROL., **6**, August 1950 and WHO/VD/SEROL., **6**, 1, September 1950).
18. *Production and Control of Cardiolipin Lecithin* (WHO/VD/SEROL., **1**, July 1950).
19. *Reference list: Bal. (British Anti-Lewisite), 2, 3-dimercaptopropanol in Toxic Manifestations Resulting from Usage of Metallic Compounds (Arsenicals, Gold, Mercury,* etc.) (WHO/VD, **58**, February 1950).
20. *Reference list: Non-specific Urethritis, Including Reiter's Disease* (WHO/VD, **65**, May 1950).
21. *Reference list: Penicillin in Early Syphilis* (WHO/VD, **60**, February 1950).
22. *Reference list: Penicillin in Latent and Late Syphilis, Including Cardiovascular Syphilis* (WHO/VD, **63**, February 1950).
23. *Reference list: Penicillin in Neurosyphilis* (WHO/VD, **61**, February 1950).
24. *Reference list: Penicillin in Syphilis—General* (WHO/VD, **59**, February 1950).
25. *Reference list: Penicillin in the Treatment of Yaws* (WHO/VD, **56**, February 1950).

Louis F. Freed.

2 Barbican Buildings,
President Street,
Johannesburg.
7 August 1951.

THE PHARMACEUTICAL REPRESENTATIVE

To the Editor: I find all the travellers who visit me charming people who have a job to do and also do it well. However, a percentage of travellers have a habit I dislike. They will extend their hand over my desk for a hearty handshake on coming in and going out. Perhaps I've got a 'thing' about it, but I'd like those travellers who have this habit to know that this Dale Carnegie act puts me off. Surely it is the host who offers his hand—if he wishes to? Having made my little grouse, I wish the travellers or propagandists, who work for the various pharmaceutical houses, 'Good Customers'.

G.P.

9 August 1951.

The Medical Association of South Africa
Die Mediese Vereniging van Suid-Afrika

AGENCY DEPARTMENT : AGENTSKAP AFDELING

KAAPSTAD : CAPE TOWN

Posbus 643, Telefoon 2-6177 : P.O. Box 643, Telephone 2-6177

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(732) Eastern Province hospital town, prescribing and dispensing solus practice. Excellent climate. One appointment. Premium £550.

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ASSISTENTE PLAASVERVANGERS VERLANG
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(689) Zululand Mission Hospital with 60 beds. Locum tenens, man or woman, for 12 to 18 months. Travelling expenses paid and furnished house available. Salary to be discussed.

(778) Noord-Kaapland. Hospitaaldorp. So spoedig moontlik vir een maand. £2 2s. p.d. plus inwoning en reiskoste. Kar word voorsien. Moontlikheid om aan te bly as assistent.

(795) Western Province town. From 30 October for 3 weeks as locum for assistant in G.P. Salary £2 2s. p.d. plus board and lodging. Car not essential.

(737) Noord-Kaapland. Vanaf 25 September vir een maand. Gewone salaris. Kar-toelae van 6d. per myl plus petrol, ens.

MEDICAL EQUIPMENT FOR SALE

(772) Strand, C.P. Couch, instrument and dressing tables, cupboards and waiting-room furniture, at approx. £100. Instruments at £100.

(758) Electrocardiograph. Sanborne Cardiette. Weight 24 lb. Perfect working condition. Used by Cape Town specialist physician. £160 or nearest offer.

(674) Complete up-to-date set of the *British Encyclopaedia of Medical Practice*. Any reasonable offer.

* * * *

JOHANNESBURG

Medical House, 5 Esselen Street. Telephones 44-9134-5, 44-0817
Mediese Huis, Esselenstraat 5. Telefone 44-9134-5, 44-0817

PRAKTYKE TE KOOP : PRACTICES FOR SALE

(Pr/S30) Johannesburg Partnership practice plus Solus practice. Mainly non-European. Present income £3,600 p.a. Premium for quick sale £1,250.

(Pr/S31) O.V.S.-praktyk. Goeie geleentheid vir algemene geneesheer met aanleg vir snywerk. Alle fasiliteite. Medisyne word aangemaak. Moet tweetalig wees. Jaarliks inkomste £2,400. Eienaar gaan verder studeer. Premie vir klandiesiewaarde, instrumente en voorrade, £1,500. Een maand introduksie sal gegee word.

ASSISTENTSKAP VERLANG : ASSISTANTSHIP REQUIRED

(A W52) Assistantship in established practice in S. Rhodesia required by married South African doctor. Qualified two years.

ASSISTENT/PLAASVERVANGER VERLANG
ASSISTANT/LOCUM REQUIRED

(L V112) Johannesburg from 18 December 1951 to 18 January 1952. £2 12s. 6d. p.d. plus all found and petrol and oil paid.

MEDICAL EQUIPMENT

(I 017) Leitz microscope £45.

(I 018) What offers? Complete set *British Encyclopaedia of Medical Practice* plus all editions of *Medical Progress* to 1950. Condition as new.

(I 019) Zeiss microscope. Condition as new. £55.

(I 020) 'Standby' model Baumanometer. £10.

(I 021) Portable Baumanometer. £3.

(I 022) Klinostik Auroscope with Ophthalmoscopic attachment. £3.

(I 023) Heavy based Irrigator stand, height adjustable, complete with glass flask and hook to carry vacolitre flasks. £7.

Provincial Administration of the Cape of Good Hope

HOSPITALS DEPARTMENT

HOSPITAL BOARD SERVICE: VACANCIES

Applications are invited for the undermentioned vacant posts in the Hospital Board Service.

The appointment of the successful candidates will be made in terms of, and be subject to, the Hospital Board Service Ordinance, 1941 (Ordinance No. 19 of 1941) and the regulations framed thereunder.

In addition to the emoluments specified hereunder, cost-of-living allowance is payable to whole-time officials and employees.

Applications should be submitted (in duplicate) on the prescribed form Staff 23, which is obtainable from the Director of Hospital Services, P.O. Box 2050, Provincial Building, Wale Street, Cape Town, or from the Branch Representative, of the Hospital Department at Cape Town, (P.O. Box 1487), Port Elizabeth (P.O. Box 80), East London (P.O. Box 13), Kimberley (P.O. Box 618), and Umtata (P.O. Box 202), or from the Medical Superintendent of any Provincial Hospital or Secretary of any School Board in the Cape Province.

The closing date for the receipt of applications is 30 September 1951 and applications should be addressed to the Branch Representative, Hospitals Department, P.O. Box 1487, Cape Town.

Institution	*Post*	*Emoluments*	*Additional qualifications and remarks*
Victoria Hospital	Medical Practitioner Grade 'A' (Surgical)	£500—600 —660—720	

Institution approved for Specialist training.

Candidates to have not less than three years' experience after graduation or two years' experience after registration.

Contract will be for a period of 4 years, subject to confirmation at the end of the first 12 months and further subject to termination at any time on 90 days' notice on either side. (12231)

Johannesburg Municipal Employees' Sick Benefit Society

SPECIALIST IN PHYSICAL MEDICINE

PART-TIME APPOINTMENT

Applications are invited for the position of part-time specialist in Physical Medicine to the Johannesburg Municipal Employees' Sick Benefit Society.

The closing date for applications will be 25 September 1951. For further particulars apply to the Secretary.

P. J. Uys
Secretary

408 P.F.A.C. Building
15 De Villiers Street
P.O. Box 2626
Johannesburg
Telephone: 33-3081

Wanted

Applications are invited for the position of assistant medical officer. The salary will be £75 (seventy-five pounds) per month with a cost-of-living allowance of £25 (twenty-five pounds) per month. In addition a free unfurnished house will be provided.

Preference will be given to a married doctor with not less than two years' practical experience.

The successful applicant will be expected to commence duty on or as soon as possible after 1 October 1951.

Full particulars concerning the appointment as well as the prescribed application form may be obtained from the Chief Medical Officer, The Mine Hospital, O'okiep Copper Co. Ltd., Nababeep, C.P.

Provincial Administration of the Cape of Good Hope

HOSPITALS DEPARTMENT

HOSPITAL BOARD SERVICE: PATHOLOGICAL LABORATORY, EAST LONDON: VACANCY FOR MEDICAL PRACTITIONER, GRADE G (PATHOLOGIST)

1. Applications are invited from registered pathologists for the post of Medical Practitioner, Grade G (pathologist) on the fixed establishment of the Pathological Laboratory, East London, with salary at the rate of £2,000 per annum (fixed).

2. The conditions of service are prescribed in terms of the Hospital Board Service Ordinance, No. 19 of 1941, and the regulations framed thereunder.

3. In addition to the scale of pay indicated a cost-of-living allowance at rates prescribed from time to time by the Administrator is payable to whole-time officials and employees (married rate £256, single £80 per annum).

4. The successful candidate, if not already in the Hospital Board Service, will be required to submit satisfactory birth and health certificates.

5. Application must be made on the prescribed form (Staff 23) which is obtainable from the Director of Hospital Services, P.O. Box 2060, Provincial Building, Wale Street, Cape Town, or from the Branch Representatives of the Hospitals Department at Cape Town (P.O. Box 1487), Port Elizabeth (P.O. Box 80), East London (P.O. Box 13), Kimberley (P.O. Box 618) and Umtata (P.O. Box 202), or from the Medical Superintendent of any Provincial Hospital or Secretary of any School Board in the Cape Province.

6. Applications must be addressed to the Director of Hospital Services, P.O. Box 2060, Cape Town, and must reach him not later than 29 September 1951. Applicants must state the earliest date on which they can assume duty.

Y249182

Provinsiale Administrasie van die Kaap die Goeie Hoop

HOSPITAALDEPARTEMENT

HOSPITAALRAADSDIENS: PATOLOGIESE LABORATORIUM, OOS-LONDEN: VAKATURE VIR GENEESHEER, GRAAD G (PATALOOG)

1. Aansoeke word ingewag van geregistreerde patoloë om die pos van Geneesheer, Graad G (patoloog) op die vaste diensstaat van die Patologiese Laboratorium, Oos-Londen, teen 'n salaris van £2,000 per jaar (vasgestel).

2. Die diensvoorwaardes word voorgeskryf ingevolge die Ordonnansie op Hospitaalraadsdiens, nr. 19 van 1941, en die regulasies wat daarkragtens opgestel is.

3. Benewens die salarisskaal soos aangedui, is 'n lewenskostetoelae betaalbaar aan voltydse beamptes en werknemers, teen bedrae wat van tyd tot tyd deur die Administrateur vasgestel word (getroude tarief £256, enkel £80 per jaar).

4. Die suksesvolle kandidaat, indien nie reeds in die Hospitaalraadsdiens nie, moet bevredigende geboorte- en gesondheidsertifikate indien.

5. Aansoeke moet gedoen word op die voorgeskrewe vorm (Staf 23) wat verkrygbaar is by die Direkteur van Hospitaaldienste, Posbus 2060, Provinsiale Gebou, Waalstraat, Kaapstad, of by die Takverteenwoordigers van die Hospitaaldepartement te Kaapstad (Posbus 1487), Port Elizabeth (Posbus 80), Oos-Londen (Posbus 13), Kimberley (Posbus 618) en Umtata (Posbus 202), of by die Mediese Superintendent van enige provinsiale hospitaal of by die Sekretaris van enige Skoolraad in die Kaapprovinsie.

6. Aansoeke moet aan die Direkteur van Hospitaaldienste, Posbus 2060, Kaapstad, gerig word, en moet hom nie later as 29 September 1951 bereik nie. Applikante moet die vroegste datum meld waarop hulle diens kan aanvaar.

Y249182

Siekefonds van die Suid-Afrikaanse Spoorweë en Hawens

AANSTELLING VAN SPOORWEGDOKTER: BOKSBURG ‚A'

Applikasies word van geregistreerde mediese praktisyns ingewag vir die betrekking van Spoorwegdokter, Boksburg ‚A', bestaande uit Boksburg-Wes, Boksburg-Noord, Boksburg-Noord hoewes (Bartlett Kleinplase, Westwood en Boksburg Kleinplase), Cason-dorpsgebied, Comet-dorpsgebied, Witfield (Lillianton), Ravenswood, Ravenswood Kleinplase, Hughes Settlements, Vogelfontein (Plantation), noord van die spoorlyn, en spoorwegtrajek Boksburg (insluitend) tot by Dunswart (uitsluitend), teen 'n salaris van £1,076 per jaar, plus gelde en toelaes wat in die regulasies van die Siekefonds voorgeskryf word, en met die reg om privaat te praktiseer.

Die salaris is onderhewig aan wysiging in ooreenstemming met die sensus van Iede wat op 1 April van elke jaar afgeneem moet word.

Die aanstelling geskied kragtens die regulasies van die Siekefonds, en opsegging van dienste is onderworpe aan vier maande kennisgewing deur een van beide partye.

Die suksesvolle applikant moet in die geneeskundige distrik woon, diens aanvaar op 'n datum wat gereël sal word, en sy pligte ooreenkomstig die regulasies van die Siekefonds uitvoer.

Aansoeke moet die Distriksekretaris, Distriksiekefondsraad, Wes-Transvaal, Kamer 342, Derde Verdieping, Nuwe Stasiegebou, Johannesburg, nie later nie as 3 Oktober 1951 bereik, en applikante moet die volgende vermeld:—

1. Volle naam.
2. Kwalifikasies (waar en wanneer verkry).
3. Ondervinding (waar en wanneer verkry en opgedoen).
4. Datum van geboorte.
5. Land van geboorte.
6. Getroud of ongetroud.
7. Of ten volle tweetalig.
8. Of Suid-Afrikaanse burger.
9. Watter staatsbetrekking, indien enige, beklee word.

Werwing deur of ten behoewe van enige applikant stel so 'n applikant bloot aan diskwalifikasie.

Enige verder besonderhede wat verlang word, kan op aanvraag van die Distriksekretaris by die bovermelde adres verkry word.

P. J. Klem
Hoofsekretaris

Johannesburg
15 September 1951 (6)

Cape Provincial Administration

HOSPITALS DEPARTMENT

Applications are invited from registered medical practitioners under the age of 60 years for appointment to the undermentioned posts on the honorary staff of the Provincial Hospital, Port Elizabeth:—

(a) Clinical Assistant to the Department of Anaesthetics.
(b) Assistant Surgeon to the Department of Ophthalmology.
(c) Registrars to the Department of Surgery (3 posts).
(d) Registrars to the Department of Medicine (2 posts).

The above appointments are subject to the Ordinance No. 18 of 1946 (Cape), as amended, and to the rules and regulations of the Department.

Applications containing full particulars of qualifications, etc., must be addressed to the Medical Superintendent of the Provincial Hospital, Port Elizabeth, to reach his office not later than 25 September 1951.

C. G. Keyter
Branch Representative

Port Elizabeth
1 September 1951 (2339)

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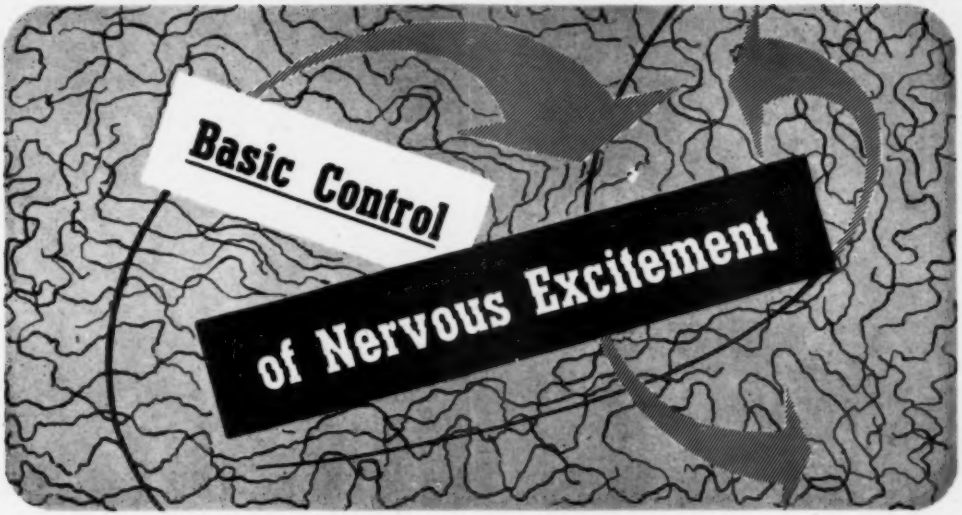

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